EXHIBIT 171

From: Fletcher, Mark P
Sent: Tuesday, August 28, 2001 3:55 PM
To: Weiner, Ethan
Subject: RE: Summary of third telecon on CLASS II issues.

Agree on your points (others made them re: lack of credibility of a 3mo program). [redacted] Non-Resp.
Non-(trying to get the study to have Nor and GI endpoints may be tough in one study, but probably needs a stat analysisi to see what power to detect events given expected rates would be for GI endpoint [redacted] Non-Resp.

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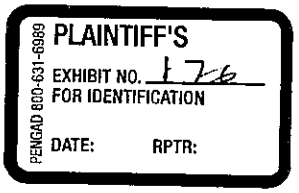

-----Original Message-----
From: Weiner, Ethan
Sent: Tuesday, August 28, 2001 9:55 AM
To: Fletcher, Mark P
Subject: RE: Summary of third telecon on CLASS II issues.

[redacted] Non-Resp. (with or without GI). The study will have no credibility without it. Second, a three month study is worthless. Having shown with CLASS that six month results can look different from one year results, will anything less than a year (especially three months) ever be taken seriously? I doubt it.

-----Original Message-----
From: Fletcher, Mark P
Sent: Monday, August 27, 2001 1:27 PM
To: Crosbie-Foote, Holly; Gavigan, Michael; Sirota, Eric; Gandelman, Mitchell
Cc: Shafner, Lori S; Weiner, Ethan
Subject: Summary of third telecon on CLASS II issues.

Brief summary of discussion re: CLASS II design:
Participants:
(Steven Cristo, Fred Begley, Jim Lefkowith, Frank Musat for a few early minutes only).

Discussed 3 possible GI outcome approaches (the latter one recently coming to Jim from Phil Needleman with positive thoughts from Carrie Cox):

Do study similar to CLASS but in non-ASA and with ibu and/or naproxen and combined endpoint- most expensive and long (4000/grp ,9mo median exposure $64M)

Do a shorter cheaper study (based on same pop and endpoints but 3mo median exposure[- 4,500 -6,000/arm and FPI-last event 6 mo; power 80-90%] ; $36- 48M)

Smaller shorter study with change in Hb/Hct(or other surrogate GI outcome measure) as primary endpoint with supporting data to argue the clinical meaningfulness of of this endpoint.

All agreed that the value and need for another events trial must be driven by what the commercial needs are for celecoxib/SCI brand and that the R&D could design and execute a trial based on what type of info(change in label, promotion only, publication, etc.) commercial feels is needed taking into consideration the overall market environment over the next 12-24 mo.

I put forward the point that I was not sure of the value of expending such a large amount of resource in the GI area vs other safety areas, but if commercials groups from both companies felt that GI safety data must be obtained and can lay out what they need, the best overall approach would be the first choice above.

As no commercial people from PFE were present I wanted to pass on what I heard.

We all agreed that additional telecon's are needed in the near future to get commercial's combined opinion on what they are looking for before we can make a final recommendation on the technical aspects of such a study.

Mark

PS,

Fred Begely also forwared Regulatory comment on the CLASS to approach(below)

----Original Message----
> From: BEGLEY, WINIFRED M. [R&D/1825]
> Sent: Monday, August 27, 2001 6:47 AM
> To: MUSAT, FRANK [GPB/USCHQP17]
> Subject: FW: Draft CLASS II comments from RA
>
> Comments from RA for today's telecon. Stephen Cristo (Pfizer) had nothing
> further to add.
> Fred
>
> -----Original Message-----
> From: ESSIG, EVA C. [R&D/1825]
> Sent: Sunday, August 26, 2001 6:06 PM
> To: BEGLEY, WINIFRED M. [R&D/1825]
> Subject: RE: Draft CLASS II comments from RA
>
> Fred,
>
> I agree with the statements below. However with regards to replication, in
> terms of endpoints I think that it could be a replicate study in the sense
> that it would be considered pivotal and the CLASS I would be considered
> supportive (since it was the "hypothesis" generating study). The fact that
> the study is only 3 months may make limit its ability to be a replicate
> study especially because FDA is as concerned about general safety as it is
> GI safety. Such a short study may not enable them to make an appropriate
> "risk/benefit analysis".
>
> Eva
> -----Original Message-----
> From: BEGLEY, WINIFRED M. [R&D/1825]
> Sent: Friday, August 24, 2001 7:18 AM
> To: ESSIG, EVA C. [R&D/1825]
> Subject: FW: Draft CLASS II comments from RA
>
> Eva,
>
> This will be discussed Monday at the telecon. Since you are out do you
> have anything to add or change?
>
> Fred
>
> ----Original Message----
> From: BEGLEY, WINIFRED M. [R&D/1825]
> Sent: Tuesday, August 21, 2001 3:05 PM
> To: ESSIG, EVA C. [R&D/1825]
> Cc: CRISTO, STEPHEN [PFIZER/Off-Site]
> Subject: Draft CLASS II comments from RA
>
> Eva, << File: CLASS II.ppt >>
> Items in bold come from the Clinical presentation to RDMC attached
> These are the draft points Stephen and I came up with, (Stephen feel free
> to modify if not adequately captured):
>
> Need for replication
> CLASS I was a large, robust trial that alone would have allowed for claims
> against tested NSAIDs had we reached the primary endpoint.

> CLASS II would not be replication since the "combined endpoint" has thus
> far not been allowed for CLASS I as it was not pre-specified, therefore it
> is not correct to state that doing CLASS II would provide replication of
> this endpoint.
>
> CLASS II could for a label change to be more definitive vs NSAIDs
> CLASS I was a huge real-life study, it is unlikely that the CLASS II data
> would negate findings in CLASS I.
>
> FDA may not be into the CLASS II study design:
> CLASS I was a real-life study and the design was considered to be
> appropriate by FDA because of the following:
> OA and RA represented
> ASA patients included
> Hard primary endpoint of UGI complications
> Long term study > 6 months allowed for seeing AEs that occur over a long
> period
>
> CLASS II may be considered inferior in design:

Non-Resp.

> Primary endpoint of combined SU and UC not a rigorous as CLASS I UGI
> complications
> Study of 3 months may not be considered long enough to see general AEs of
> importance, not just GI AEs.
> FDA has a concern that celecoxib may not show the possibility of ulcer
> complications in the long term if we only do a 3 month study (i.e.
> diclofenac patients dropped due to symptoms but celecoxib didn't and went
> on to complications, FDA are concerned that with celecoxib there is no
> early warning as there is for diclofenac).

Non-Resp.

>
> Diclofenac as a comparator
> Diclofenac was included mainly for ex-US use. CLASS data has not been
> embraced by ex-US markets so why repeat?
>
> Time to an approval
> Time to decision and study start, unknown?
> Estimate clinical study 6-12 months
> FDA review time 10-12 months
> Therefore time to changed label could be 2-3 years off. Commercial to
> assess value given this timing.
>
> Anything you can add?

> Fred

****

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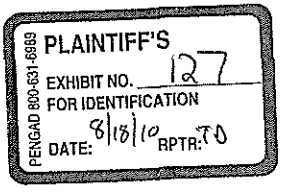
EXHIBIT 172

From: Weiner, Ethan
Sent: Tuesday, February 05, 2002 1:01 AM
To: Loose, Leland D; Zwillich, Samuel H; Gilbertsen, Richard
Cc: 'Jing Cao (E-mail)'
Subject: CBX-0051397_ RE: Ethan's clinical plan for S2474



Agree -- would not do them for a new candidate at this time.

-----Original Message-----
From: Loose, Leland D
Sent: Monday, February 04, 2002 4:10 PM
To: Zwillich, Samuel H; Gilbertsen, Richard
Cc: 'Jing Cao (E-mail)'; Weiner, Ethan
Subject: RE: Ethan's clinical plan for S2474

As has been reported to the agency and in the lay press, CLASS had about 8,000 patients and ran for about a year with a cut of data at 6 months, cost much greater than your 30M though. If you look at labels all of these big ticket studies got a big goose egg so I don't see their value yet. Leland

-----Original Message-----
From: Zwillich, Samuel H
Sent: Monday, January 28, 2002 3:28 PM
To: Gilbertsen, Richard; Loose, Leland D
Cc: 'Jing Cao (E-mail)'; Weiner, Ethan
Subject: RE: Ethan's clinical plan for S2474

Rick:

In light of the publicly available outcomes of the CLASS (Celebrex vs. diclofenac and ibuprofen) and VIGOR (Vioxx vs. naproxen) studies, this study outline from 1998 would need to be re-thought, including phase, population, comparators, endpoints. But I agree that costs would likely be > $30 million. As Ethan wrote : "Much has happened since then," and time wounds all heels and all good CDPs, too. Let's first see how badly it has wounded S2474!

Samuel H. Zwillich
Clin Dev / PII
Tel (860) 732-4645
Fax (860) 715-8618

-----Original Message-----
From: Gilbertsen, Richard
Sent: Monday, January 28, 2002 1:38 PM
To: Loose, Leland D; Zwillich, Samuel H
Cc: Jing Cao (E-mail)
Subject: Ethan's clinical plan for S2474

Leland, Sam,

Just curious about a couple of aspects of the clinical trials. In Study 4b(1), which is a Phase III GI study in RA and OA, the total number of patients on drug (any of the controls or S) is 6,000 for 6 months. For one thing, shouldn't there be a placebo group here or are historic data sufficient for GI effects?

Of more interest to me, is 6,000 the number of patients who must complete the 6-month trial, or the number enrolled, which takes into consideration a certain expected dropout rate? I was looking at the cost figures and wondering how much patients are paid who drop out during a study...probably more $$ the longer they last (???). If the dropout rate was higher than expected (perhaps solely because of, e.g., endoscopy), and if the number 6,000 is the number of patients who must complete the trial, then the total number of patients and total cost could be well above $ 30M. Is this correct? This obviously applies to patient numbers for all the studies.

Thanks for any feedback.

Confidential - Subject To Protective Order

Rick

Tracking:

Recipient	Message Status
Loose, Leland D	Read: 2/5/2002 4:59 PM
Zwillich, Samuel H	Read: 2/5/2002 3:15 PM
Gilbertsen, Richard	Read: 2/5/2002 1:07 PM
'Jing Cao (E-mail)'	Delivery Failed: 2/5/2002 12:01 PM

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EXHIBIT 173

12 of 28 DOCUMENTS

Copyright 2001 Times Newspapers Limited
Sunday Times (London)

August 12, 2001, Sunday

SECTION: Home news

LENGTH: 286 words

HEADLINE: Move to open all drug test results

BYLINE: Jonathan Leake and Kevin Dowling

BODY:

THE world's most prominent medical journals, including The Lancet and the British Medical Journal, have joined forces to stop drug firms "cheating" on medical studies and refusing to publish bad results.

The move follows a case where Pharmacia, which owns Monsanto, the GM seed firm, last year was accused of duping the Journal of the American Medical Association (JAMA) into publishing favourable results from a study of the arthritis drug **Celebrex.**

The six-month study on 8,000 patients claimed **Celebrex** was associated with lower rates of stomach and intestinal ulcers than two other older arthritis medicines. In fact, the study took a year and the final results showed that almost all of the ulcer complications occurring in the second, unpublished half, were in **Celebrex** users.

Medical editors around the world will now refuse from next month to print drug-company sponsored studies unless the researchers involved are guaranteed scientific independence. One described the action as an attempt to "give scientists clout with drug companies".

Dr **Michael Wolfe,** an American expert in the field, who had given the study a favourable review in the JAMA, said: "I thought I was looking at a completely different study. The politically correct term is data discrepancy -but I call it scientific fraud. I believe Pharmacia cheated."

Steven Geis, a vice-president for clinical research of Pharmacia and one of the authors of the study, said that only the first six months of data were presented because, after that, more patients withdrew from the comparison groups than from the **Celebrex** group, biasing later findings. "The intention really was not to be deceptive in any way," he said.

LOAD-DATE: August 13, 2001

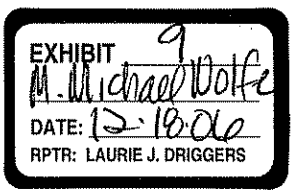


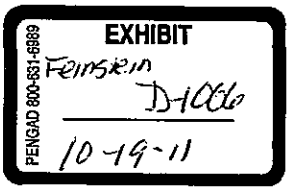
EXHIBIT 174

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-998/S-009



G.D. Searle L.L.C.
Attention: Eva Essig, Ph.D.
Associate Director, Global Regulatory Affairs
4901 Searle Parkway
Skokie, IL 60077

Dear Dr. Essig:

Please refer to your supplemental new drug application dated June 12, 2000, received June 14, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celebrex™ (celecoxib capsules) Capsules, 100 mg and 200 mg.

We acknowledge receipt of your submissions dated February 04; March 21; April 08, 17, and 23; May 01, 09, and 17, 2002. Your submission of December 20, 2001 constituted a complete response to our April 12, 2001 action letter.

This supplemental new drug application provides for changes to the **Warnings, Precautions, Adverse Events,** and **Clinical Studies** sections of the labeling based on a large gastrointestinal outcome study for Celebrex.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-998/S-009." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Barbara Gould, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Lawrence Goldkind, M.D.
Deputy Division Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

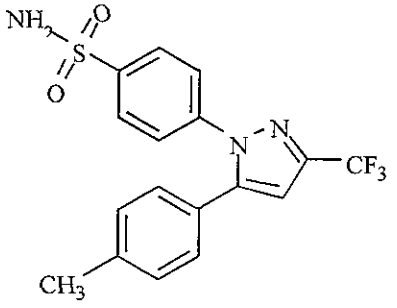
/s/

Lawrence Goldkind
6/7/02 09:16:32 AM

CELEBREX®
(celecoxib capsules)

DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. It has the following chemical structure:



The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

CELEBREX oral capsules contain 100 mg and 200 mg of celecoxib.

The inactive ingredients in CELEBREX capsules include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: CELEBREX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

Pharmacokinetics:

Absorption
Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID; at higher doses there are less than proportional increases in Cmax and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 1.

Table 1: Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
Cmax, ng/mL	**Tmax, hr**	**Effective t1/2, hr**	**Vss/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1] Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects
When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC. CELEBREX, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should be administered with food to improve absorption.

Distribution
In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion
Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special Populations

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

Pediatric: CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

Race: Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Insufficiency: A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class II) hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended.

Renal Insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CELEBREX is not recommended in patients with severe renal insufficiency (see WARNINGS - Advanced Renal Disease).

Drug Interactions

Also see **PRECAUTIONS – Drug Interactions.**

General: Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA): CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg BID and 200 mg BID provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BID or 200 mg QD.

Rheumatoid Arthritis (RA): CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg BID and 200 mg BID were similar in effectiveness and both were comparable to naproxen 500 mg BID.

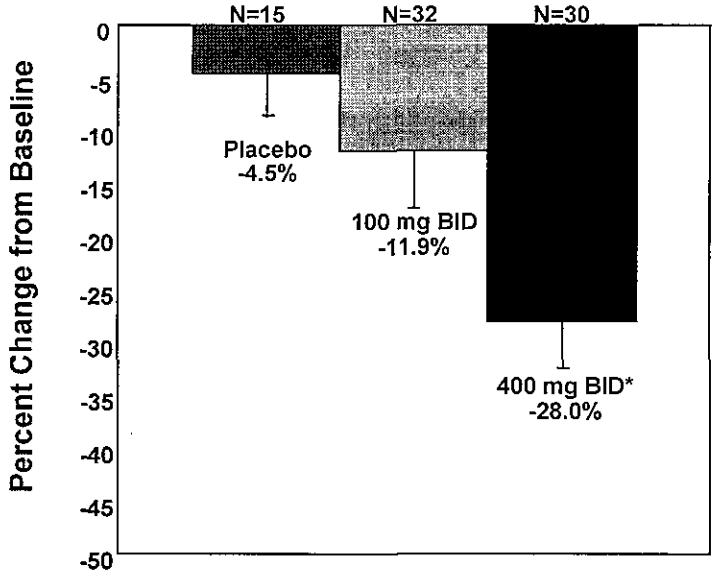
Although CELEBREX 100 mg BID and 200 mg BID provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional benefit above that seen with 100-200 mg BID.

Analgesia, including primary dysmenorrhea: In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses (see DOSAGE AND ADMINISTRATION) of CELEBREX provided pain relief within 60 minutes.

Familial Adenomatous Polyposis (FAP): CELEBREX was evaluated to reduce the number of adenomatous colorectal polyps. A randomized double-blind placebo-controlled study was conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg BID, 12% for CELEBREX 100 mg BID and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg BID was statistically superior to placebo at the six-month timepoint (p=0.003). (See Figure 1.)

Figure 1
Percent Change from Baseline in Number of Colorectal Polyps (FAP Patients)



*** p=0.003 versus placebo**

Special Studies

Endoscopic studies: Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials using active comparators, two of which also included placebo controls. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX over the range studied.

Table 2 summarizes the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Table 2
Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients

	3-Month Studies	
	Study 1 (n = 1108)	**Study 2 (n= 1049)**
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	---
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs. all other treatments

Table 3 summarizes data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Table 3
Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients

	Week 4	Week 8	Week 12	Final
Study 3 (n=523)				
Celebrex 200 mg BID	4.0% (10/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BID	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
Study 4 (n=1062)				
Celebrex 200 mg BID	3.9% (13/337)†	2.4% (7/296)†	1.8% (5/274)†	7.0% (25/356)†
Diclofenac 75 mg BID	5.1% (18/350)	3.3% (10/306)	2.9% (8/278)	9.7% (36/372)
Ibuprofen 800 mg TID	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3% (78/334)

*p≤ 0.05 Celebrex vs. naproxen based on interval and cumulative analyses
†p≤ 0.05 Celebrex vs. ibuprofen based on interval and cumulative analyses

One randomized and double-blind 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking CELEBREX 200 mg BID was 4% vs 15% for patients taking diclofenac SR 75 mg BID ($p<0.001$).

In 4 of the 5 endoscopic studies, approximately 11% of patients (440/4,000) were taking aspirin (≤ 325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

The correlation between findings of endoscopic studies, and the relative incidence of clinically significant serious upper GI events has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials, albeit infrequently (see *Use with Aspirin* and WARNINGS-Gastrointestinal (GI) Effects).

Use with Aspirin: The Celecoxib Long-Term Arthritis Safety Study (CLASS) was a prospective long-term safety outcome study conducted postmarketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg TID or diclofenac 75 mg BID (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The Kaplan-Meier cumulative rates at 9 months are provided for all analyses. The

primary endpoint of this outcome study was the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of *complicated ulcers* between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant. Those patients on CELEBREX and concomitant low-dose ASA experienced 4-fold higher rates of *complicated ulcers* compared to those not on ASA (see WARNINGS-Gastrointestinal (GI) Effects). The results for CELEBREX are displayed in Table 4. For *complicated and symptomatic ulcer* rates, see WARNINGS-Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation).

Table 4
Effects of Co-Administration of Low-Dose Aspirin on *Complicated Ulcer* Rates with CELEBREX 400 mg BID (Kaplan-Meier Rates at 9 months [%])

	Non-Aspirin Users n=3105	Aspirin Users n=882
Complicated Ulcers	0.32	1.12

Platelets: In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

INDICATIONS AND USAGE

CELEBREX is indicated:

1) For relief of the signs and symptoms of osteoarthritis.

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

3) For the management of acute pain in adults (see CLINICAL STUDIES).

4) For the treatment of primary dysmenorrhea.

5) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance , surgery).

It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients . It is also not known whether the effects of CELEBREX treatment will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX treatment in patients with FAP beyond six months have not been studied (See CLINICAL STUDIES, WARNINGS, and PRECAUTIONS sections).

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation:
Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms (see PRECAUTIONS-Hematological Effects). Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

CLASS Study: The estimated cumulative rates at 9 months of *complicated and symptomatic ulcers* (an adverse event similar but not identical to the "upper GI ulcers, gross bleeding or perforation" described in the preceding paragraphs) for patients treated with CELEBREX 400 mg BID (see Special Studies- *Use with Aspirin*) are described in Table 5. Table 5 also displays results for patients less than or greater than or equal to the age of 65 years. The differences in rates between the CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

Table 5
***Complicated and Symptomatic Ulcer* Rates in Patients Taking CELEBREX 400 mg BID (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors**

	Complicated and Symptomatic Ulcer Rates
All Patients	
Celebrex alone (n=3105)	0.78
Celebrex with ASA (n=882)	2.19
Patients < 65 Years	
Celebrex alone (n=2025)	0.47
Celebrex with ASA (n=403)	1.26
Patients ≥ 65 Years	
Celebrex alone (n=1080)	1.40
Celebrex with ASA (n=479)	3.06

In a small number of patients with a history of ulcer disease, the *complicated and symptomatic ulcer* rates in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease (see WARNINGS- Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation).

Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic

patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX, is not recommended in these patients with advanced kidney disease. If CELEBREX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

Pregnancy

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Familial Adenomatous Polyposis (FAP): Treatment with CELEBREX in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of CELEBREX. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

PRECAUTIONS

General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX (see ADVERSE REACTIONS – post-marketing experience). In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo,

and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS-Advanced Renal Disease).

Hematological Effects: Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials, the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES-Special Studies-Platelets).

Fluid Retention, Edema, and Hypertension: Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). In the CLASS study (see Special Studies-*Use with Aspirin*), the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg TID and diclofenac 75 mg BID were 4.5%, 6.9% and 4.7%, respectively. The rates of hypertension in the CELEBREX, ibuprofen and diclofenac treated patients were 2.4%, 4.2% and 2.5%, respectively. As with other NSAIDs, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients: CELEBREX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects-Risk of Gastrointestinal Ulceration, Bleeding, and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.
Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Patients with familial adenomatous polyposis (FAP) should be informed that CELEBREX has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX.

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

Drug Interactions
General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin: CELEBREX can be used with low-dose aspirin. However, concomitant administration of aspirin with CELEBREX increases the rate of GI ulceration or other complications, compared to use of CELEBREX alone (see CLINICAL STUDIES - Special Studies – *Use with Aspirin* and WARNINGS – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation – CLASS Study).

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see Pharmacokinetics - Metabolism). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

Carcinogenesis, mutagenesis, impairment of fertility: Celecoxib was not carcinogenic in rats

given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C. Celecoxib at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID) throughout organogenesis. There are no studies in pregnant women. CELEBREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided.

Labor and delivery: Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

Nursing mothers: Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use
Of the total number of patients who received CELEBREX in clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients (see WARNINGS – Gastrointestinal (GI) Effects -Risk of GI Ulceration, Bleeding, and Perforation).

ADVERSE REACTIONS

Of the CELEBREX treated patients in the premarketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients received CELEBREX at these doses for 6 months or more; approximately 2,300 of these received it for 1 year or more and 124 of these received it for 2 years or more.

Adverse events from CELEBREX premarketing controlled arthritis trials: Table 6 lists all adverse events regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

Table 6
Adverse Events Occurring in ≥ 2% Of Celebrex Patients From CELEBREX Premarketing Controlled Arthritis Trials

	Celebrex (100-200 mg BID or 200 mg QD) (n=4146)	Placebo (n=1864)	Naproxen 500 mg BID (n=1366)	Diclofenac 75 mg BID (n=387)	Ibuprofen 800 mg TID (n=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.
The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

	Celebrex (100 - 200 mg BID or 200 mg QD)
Gastrointestinal:	Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting
Cardiovascular:	Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction
General:	Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Resistance mechanism disorders:	Herpes simplex, herpes zoster, infection bacterial, infection, fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
Central, peripheral nervous system:	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo
Female reproductive:	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis
Male reproductive:	Prostatic disorder
Hearing and vestibular:	Deafness, ear abnormality, earache, tinnitus
Heart rate and rhythm:	Palpitation, tachycardia
Liver and biliary system:	Hepatic function abnormal, SGOT increased, SGPT increased
Metabolic and nutritional:	BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
Musculoskeletal:	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
Platelets (bleeding or clotting):	Ecchymosis, epistaxis, thrombocythemia
Psychiatric:	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Hemic:	Anemia
Respiratory:	Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
Skin and appendages:	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash, maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application site disorders:	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special senses:	Taste perversion
Urinary system:	Albuminuria, cystitis, dysuria, hematuria, micturition, frequency, renal calculus, urinary incontinence, urinary tract infection
Vision:	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality:
The following serious adverse events have occurred rarely in patients taking CELEBREX. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis*

Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus
Liver and biliary system:	Cholelithiasis, *hepatitis, jaundice, liver failure*
Hemic and lymphatic:	Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia*
Metabolic:	*Hypoglycemia, hyponatremia*
Nervous system:	*Aseptic meningitis,* ataxia, suicide;
Renal:	Acute renal failure, *interstitial nephritis*
Skin:	*Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*
General:	Sepsis, sudden death, *anaphylactoid reaction, angioedema*

Safety Data from CLASS Study:

Hematological Events:
During this study (see Special Studies-*Use with Aspirin*), the incidence of clinically significant decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP) compared to patients on either diclofenac 75 mg BID or ibuprofen 800 mg TID: 0.5%, 1.3% and 1.9%, respectively. The lower incidence of events with CELEBREX was maintained with or without ASA use (see CLINICAL STUDIES- Special Studies- Platelets).

Withdrawals/Serious Adverse Events:
Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for CELEBREX, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e. those causing hospitalization or felt to be life threatening or otherwise medically significant) regardless of causality were not different across treatment groups, respectively, 8%, 7%, and 8%.

Based on Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events*, there were no differences between the CELEBREX, diclofenac or ibuprofen treatment groups. The rates in all patients at 9 months for CELEBREX, diclofenac and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The rates for non-ASA users in each of the three treatment groups were less than 1%. The rates for myocardial infarction in each of the three non-ASA treatment groups were less than 0.2%.

*includes myocardial infarction, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks or ischemic cerebrovascular accidents.

Adverse events from analgesia and dysmenorrhea studies: Approximately 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery

pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

Adverse events from the controlled trial in familial adenomatous polyposis: The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

OVERDOSAGE

No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity.

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be sought for each patient. These doses can be given without regard to timing of meals.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

Management of Acute Pain and Treatment of Primary Dysmenorrhea: The recom-mended dose of CELEBREX is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Familial adenomatous polyposis (FAP): Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg (2 X 200 mg capsules) twice per day to be taken with food.

Special Populations

***Hepatic insufficiency*:** The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class II) should be reduced by approximately 50% (see CLINICAL PHARMACOLOGY – Special Populations).

HOW SUPPLIED

CELEBREX 100-mg capsules are white, reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025-1520-31	bottle of 100
0025-1520-51	bottle of 500
0025-1520-34	carton of 100 unit dose

CELEBREX 200-mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025-1525-31	bottle of 100
0025-1525-51	bottle of 500
0025-1525-34	carton of 100 unit dose

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Rx only **Revised: 6/7/02**

Manufactured for: G.D. Searle LLC
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Searle **Pfizer**

CELEBREX®
(celecoxib capsules)

(A05264-)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Goldkind
6/7/02 09:16:32 AM

EXHIBIT 175

22 of 25 DOCUMENTS

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BusinessWeek
Business Week

June 24, 2002

SECTION: SCIENCE & TECHNOLOGY; COMMENTARY; Number 3788; Pg. 78

LENGTH: 845 words

HEADLINE: THE CREDIBILITY GAP IN DRUG RESEARCH

BYLINE: By Paul Raeburn; Raeburn covers science and medicine in New York.

BODY:

It's supposed to be the gold standard of medical research: Doctors randomly split research subjects into two groups, with some getting a new drug, others a sugar pill. To avoid any bias, the researchers don't know who's getting what. This ritual -- the randomized, double-blind clinical trial -- often takes years and costs tens of millions of dollars, but it produces clear, unbiased data on the benefits of drugs.

At least that's the way it's supposed to work. In fact, the reports of those results are often misleading or incomplete. On June 1, the British Medical Journal published a report critical of a Pharmacia Corp.-funded study of its $ 3 billion-dollar-a-year arthritis drug, **Celebrex.** The report claimed the study's favorable results omitted contradictory data. And on June 5, The Journal of the American Medical Assn. (JAMA) published a series of reports critical of the way trials are done and reported, and the way conclusions are often couched to make new treatments seem better than they are.

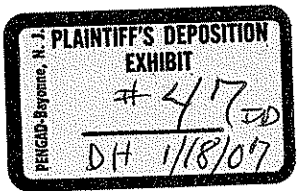
The **Celebrex** case illustrates one such problem. The study, reported in JAMA by company-funded researchers two years ago, concluded the drug was associated with fewer ulcers and ulcer complications than two other drugs, ibuprofen and diclofenac. The British Medical Journal says the article was misleading because it omitted data that found no safety benefit for **Celebrex.** (The additional data were later made public at a Food & Drug Administration advisory committee meeting.)

G. Steven Geis, Pharmacia's vice-president for research, says information was omitted only because it was not reliable. On June 7, however, the FDA decided, using all the data, that the study "did not show a safety advantage in upper gastrointestinal events for **Celebrex.**"

Critics blame industry sponsorship for these problems. It is not only the published studies that cause concern but also the studies that never appear, says Dr. **Drummond Rennie,** a deputy editor at JAMA and professor at the University of California at San Francisco. When a study starts going wrong, its sponsor may be tempted "to stomp on the investigators and say, 'You must keep this quiet.'" And "companies have yielded to that temptation," he says. Others agree. "In situations when there are large economic interests, you just cannot be sure whether the problems in the trial have been resolved in a fair way," says the author of the British Medical Journal article, Dr. Peter Juni of the University of Bristol in Britain and the University of Berne in Switzerland.

"That's not true," says Mark Grayson, a spokesman for the Pharmaceutical Research & Manufacturers of America. Drugmakers support efforts to assure the independence of academic researchers who participate in industry-sponsored trials, he says.

Rennie thinks editors at the prestigious medical journals are getting better at policing these issues. He is still rankled, however, by JAMA's publication of the **Celebrex** study. The study's authors, including Pharmacia, "were not open with us," he says. "They signed letters saying the studies have all the relevant stuff," but "they had contradictory results



when they sent us this paper, and they should have revealed them to us. And they didn't." Says Pharmacia's Geis: "We've tried to work real hard with JAMA to resolve any misunderstanding. We value JAMA."

Rennie says universities and their researchers must insist on guarantees from company sponsors that the results can be freely reported. Juni says the industry could fund an independent agency to finance studies. The FDA, which often has more data than the journals, does point out discrepancies, says Dr. Sandra Kweder, deputy director of the FDA's Office of New Drugs. But "it's difficult for us to police every potential journal," she says. "We don't have a department of journal review to catch those things."

The aim is to restore confidence in the findings of medical studies. As was the case with **Celebrex,** these studies are often widely circulated in the medical community. Many doctors begin prescribing drugs based on the findings, before the FDA rules on whether the studies have met its standards. If confidence in the veracity of medical research is lost, however, it is the pharmaceutical industry that will suffer.

Weird Science
Here are some of the criticisms made by research authorities who, in the June 5 Journal of the American Medical Assn., reviewed the quality of current medical research literature
-- Studies often fail to put results in the context of previous studies
-- Authors of studies do not adequately address legitimate scientific criticism after publication, and journal editors do not require them to do so
-- Study collaborators frequently disagree about their study's conclusions, and the published reports often fail to represent the full range of authors' opinions
-- Guidelines showing how results ought to be reported are often ignored or badly applied

URL: http://www.businessweek.com/index.html

GRAPHIC: Photograph: **CELEBREX** A Pharmacia-funded study is under fire

LOAD-DATE: June 20, 2002

EXHIBIT 176

From: lsimon@bidmc.harvard.edu
Sent: Tuesday, December 09, 2003 10:10 PM
To: Gail.Cawkwell@pfizer.com
Subject: BXT-0282979_RE: CLASS

BXT-0282980_newc elecoxibmanusc...

well, Gail the CLASS trial data has been submitted and here it is, I hope you like it, Lee

-----Original Message-----
From: Cawkwell, Gail
To: 'lsimon@bidmc.harvard.edu'
Sent: 12/9/2003 1:17 PM
Subject: CLASS

Lee, I seem to communicate with you from lovely European capitols only.... I am in Rome this week on business, and hoping for an update of the CLASS manuscript. We last talked a month ago at which point some tables/figures needed some work but it was close to submission!

I also have a request. We have a submission due to the UK NICE commission late in January, and we are hoping that we can include a copy of the submitted manuscript to them, as a confidential document, noting that it has been submitted but not yet reviewed. I am happy to provide you with any additional details, but would like your permission along with the other authors, to do this.

Looking forward to hearing from you!
Best wishes,

Gail D. Cawkwell, MD, PhD
Medical Director, Pain and Inflammation
Medical Team Leader, Celebrex World Wide Pfizer, Inc New York, NY

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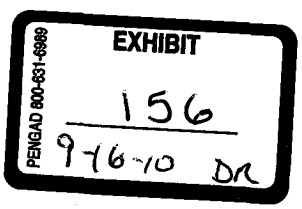

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CLASS: The Celecoxib Long Term Arthritis Safety Study: An Assessment of Analytical Methods

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Running Title: CLASS: An Assessment of Analytical Methods

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Key words: celecoxib nonsteroidal anti-inflammatory drugs gastrointestinal safety

Word count: 2430

Abstract

Context:

The Celecoxib Long-Term Arthritis Safety Study (CLASS), a double blind, multicenter, RCT comparing incidence of ulcer complications (POB's: primary outcome) and secondary, symptomatic ulcers (PUB's) in 7968 osteoarthritis and rheumatoid arthritis patients receiving celecoxib 400 mg BID, diclofenac 75 mg BID or ibuprofen 800 mg TID,

Objective:

Comparison of primary and secondary endpoints over entire trial (median exposure of 9 months) with published data at 6 months.

Methods:

Analyses used the intent to treat population, chi-square for categorical data, non-parametric tests for continuous variables and log rank test for time to event curves. Hazard and cumulative hazard function analyses examined the extent to which risk of an event changed over time.

Results:

With celecoxib: POB's over entire trial and 6 months were 0.73 vs. 0.76 events /100 patient years, respectively, p=NS; in combined NSAID groups: POB's declined after 6 months [1.45 at 6 months vs. 0.95 events/100 patient years (p=0.016)]. POB's with celecoxib vs combined NSAIDs: at 6 months, p=0.09; over entire trial p=0.45. PUB's with celecoxib were 2.08/100 patient years at 6 months vs 1.85 over entire trial. (p=0.010); in combined NSAIDs: PUB's 3.54/100 patient years at 6 months; 2.81 over entire trial ($p \leq 0.04$, celecoxib vs. NSAIDs at both timepoints). A statistical difference between celecoxib and NSAIDs for PUB's at 6 months was sustained over the entire trial (p=0.04). Early withdrawals occurred with diclofenac treatment for GI adverse events [22%], liver function tests > 3XULN [3.5%], and ibuprofen for lack of efficacy [17%].

Conclusions:

CLASS failed to demonstrate statistical significance between celecoxib and combined NSAIDs by POBs, although statistically significant for PUBs at 6

months and trial endpoint. These study results are likely due to 3 flaws in trial design: insufficient power; increased use of low dose aspirin and unexpected early withdrawals in NSAID treatment arms.

WORD COUNT: 297

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used class of therapeutics. Effective as analgesics, anti-inflammatory and anti-pyretic agents, they are believed predominantly to act by inhibiting the cyclooxygenase (COX) enzymes. Inhibition of COX activity may also lead to their well-characterized risk profile (1-3).

Since 1989 it has been established that at least two COX enzymes result in prostaglandin formation (4-6). In general, COX-2 activity is inducible and is important in mediating pain and inflammation; whereas COX-1 activity is constitutive in most organ systems and includes maintenance of homeostasis in the gastrointestinal (GI) mucosa. In certain tissues, COX-2 production is also constitutive (7,8). Although endoscopy studies demonstrated that fewer gastro-duodenal ulcers occurred with COX-2 selective NSAIDs than active comparators including diclofenac, naproxen, and ibuprofen in patients with osteoarthritis [OA] and rheumatoid arthritis [RA] (9-11), it remains to be proven that endoscopic results predict fewer clinically important GI adverse outcomes. Therefore the first approved selective COX-2 inhibitors, celecoxib and rofecoxib were studied in large GI outcome trials, CLASS and VIGOR, respectively (12, 13).

In the CLASS trial, 7968 patients with OA or RA were enrolled in two large, double blind randomized controlled trials (RCTs) and received 2-4 times the recommended dose of celecoxib (400 mg BID) or standard doses of NSAIDs: ibuprofen 800 mg TID or diclofenac 75 mg BID using equal randomization. It was prospectively defined that data from both RCTs would be combined. Cardiovascular prophylaxis with low dose aspirin (ASA) ($\leq$ 325 mgs/day) was allowed. The primary endpoint was time to occurrence of GI complications including perforations, obstructions, or bleeds (POBs). A secondary outcome was time to occurrence of symptomatic ulcers, perforations, obstructions and bleeds (PUBs). The intent to treat population was all patients randomized who received

at least one dose of study medication. Data Safety Monitoring and GI Adjudication Committees reported to a supervisory Executive Committee, each of which adjudicated GI events in blinded fashion.

The trial was designed to provide at least 6 months exposure for all patients and was expected to result in approximately 12 months treatment in the majority of the patients. Documentation of ulcers were based on symptomatic reports as no formal screening with endoscopy was required before or during the trial. The statistical analysis plan predefined comparison of primary and secondary outcomes in patients receiving aspirin compared with non-ASA users.

When accumulation of new GI complications slowed and few events were noted over a 3-month period both DSMC and Executive Committees recommended early termination of the trial. Based on blinded review of the combined data across treatment groups, it was evident that the GI event rate had become negligible and the drop-out rate past 6 months exceeded 50%. It was determined that data from the first 6 months of the RCT were most representative for determining the causal association between treatment and adverse GI outcomes. Prior to unblinding, both oversight committees recommended that 6 month data be the primary analysis for publication The median duration of protocol participation was 9 months, although some patients received treatment as long as 15 months. As published (12) at 6 months there was a non-significant trend ($p=0.09$) for a lower incidence of GI complications (POBs) with celecoxib than combined NSAID treatment. The secondary endpoint of symptomatic ulcers, perforations, and bleeds (PUBs) significantly favored treatment with celecoxib ($p=0.04$), compared with combined NSAIDs.

The rationale for selecting 6 month data for initial publication included: 1) few GI complications were reported after 6 months of protocol participation when drop out rates exceeded 50%, 2) only a limited number of patients with risk factors for NSAID-induced upper GI complications remained in the trial after that time, 3) the

enrolled patient population had fewer risk factors for GI complications than anticipated, and 4) more were receiving cardiovascular doses of aspirin (ASA).

Furthermore, after the blinded review was completed, it was subsequently discovered that more than the expected treatment discontinuations for GI adverse events occurred in patients receiving diclofenac and for lack of efficacy in the ibuprofen treatment group. As data after 6 months of protocol treatment were not derived from the same patient population as initially enrolled, there was concern that the integrity of the randomization process would not be preserved when comparing causality in the remaining patient population. This has been referred to as informative censoring (15-17).

Experimental Methods

The primary outcome in the CLASS trial was the incidence of ulcer complications: perforation, obstructions, and bleeds (POBs). (12). The secondary outcome measure: incidence of symptomatic ulcers (perforations, ulcers and bleeding (PUBs) was identical to the primary endpoint in the VIGOR trial (13). The predetermined statistical analysis plan included evaluating the results in patients with and without the use of concomitant low dose aspirin The following analyses report data over the entire treatment period.

Analysis of the intent to treat population used standard methods for comparison between groups including chi-square tests for categorical data and non-parametric tests for comparative analyses of continuous variables. Time to event data were displayed using the Kaplan Meier method. Start time used date of randomization and end date onset of a predefined GI outcome if it occurred (i.e. uncensored value). Last date of follow-up was utilized when additional data were censored due to trial completion (censored value). Hazard and cumulative hazard function analysis examined the extent to which risk of an event increased or decreased (remained constant) over time (18). Hazard functions were

smoothed to aid in identifying the true risk pattern while reducing random variation (18,19) Comparisons of time to event curves were performed using log-rank tests (17-20). Annualized incidence rates summarize the information for each treatment group. Within group comparisons of event rates for different time periods are based on conditional independent increments in a Poisson process. All p values are two sided.

This manuscript has been prepared by clinical investigators and members of the DSMC and the Executive Committee for CLASS. No one who was an employee of the sponsor of this trial participated in the overall analysis of these data or the preparation of this report.

Results

Treatment disposition is presented in Table 1. Patient demographics and known risk factors are shown in Table 2. Fewer patients than expected were enrolled with identified risks for GI complications.

Figure 1 (top panel) shows results for the primary endpoint at 6 months and over the entire trial shows a non-statistically significant trend for a lower incidence of GI complications: POBs, the primary outcome, in the celecoxib versus combined NSAID treatment groups (p=0.45) over the entire trial [long term results] compared with published 6 month data (p=0.09) (12). Within the celecoxib treatment group, the incidence of POBs over the entire trial and at 6 months were nearly identical (0.73 vs 0.76 events per 100 patients years). In contrast, there was a decline in the incidence of POBs after 6 months in the combined NSAID treatment group (1.45 at 6 months vs 0.95 events per 100 patient years over the entire trial [p=0.016]), also evident when the NSAID treatment groups are examined separately [data not shown]. The incidence of POBs in patients who were not receiving ASA (78% of the ITT population) is shown at the bottom panel of Figure 1. In this predefined analysis of non aspirin users, the incidence of POB's with celecoxib was 0.44/100 patient years at 6 months and trial endpoint

vs. 1.27 and 0.82, respectively with combined NSAIDs. A statistically significant treatment difference between celecoxib and NSAID treatment groups is not evident over the entire trial (log rank p=0.19) although different at 6 months (log-rank p=0.04).

A decline in the rate of POBs over time is evident in the active comparator but not celecoxib treatment groups. Reanalysis of these data explored the extent to which early treatment discontinuations explain this differential decline. As shown in the Kaplan-Meier curves in Figure 2, no further POBs were observed in the diclofenac treatment group after 80 days (top panel) and in those not receiving ASA after 60 days (bottom panel).

Figure 3 presents the secondary endpoint, PUBs, in the ITT population (top panel) and non-ASA users (bottom panel), respectively. Over the entire trial and at 6 months, celecoxib administration was associated with a statistically significant lower incidence of PUBs compared with combined NSAID treatment groups ($p \leq 0.04$ for both comparisons). The rate for PUBs in all patients receiving celecoxib was 1.85 over the entire trial and 2.08 per 100 patient years at 6 months (p=NS). In the combined NSAID group the rate for PUBs was 2.81 over the entire trial; less than 3.54 per 100 patient years observed at 6 months (p=0.010).

In patients receiving celecoxib without low dose ASA, the event rate of POBs over the entire trial was 0.32 and PUBs: 0.78 per 100 patient years (21). In the combined NSAID group, the incidence of POBs was 0.95 and PUBs, 1.85 per 100 patient years, compared with an expected rate of 1-2% for POBs and 2-4% for PUBs with non-selective NSAIDs,.

A higher proportion of patients discontinued treatment early in the combined NSAID group when compared with celecoxib treatment (Figure 4). Specifically, more patients withdrew with diclofenac treatment due to the adverse events,

primarily due to complaints of abdominal pain (a), dyspepsia (b), nausea (c), and diarrhea (data not shown) (Figure 5). Overall 22% of patients receiving diclofenac discontinued protocol treatment associated with adverse GI events, and an additional 3.5% due to liver function test elevations > 3 times the upper limit of normal, as required by protocol. Both withdrawal rates were statistically significant compared with celecoxib and ibuprofen treatment arms. In contrast, 17% of patients in the ibuprofen group withdrew due to lack of efficacy (Figure 5).

It appears that patients at risk for GI complications differentially discontinued treatment early, and were thereby "prevented" from developing a primary or secondary GI outcome. Figures 6 and 7 indicated that time from patient reported abdominal pain or dyspepsia to treatment discontinuation was very short (most patients withdrew within 2.5 weeks of onset of symptoms), and the 45 degree line (panel B in each figure) indicates the two events (onset of symptomatic GI adverse event and drop out) coincide with each other. The nature and extent to which this "informative censoring" altered the patient population at risk over time in the protocol, and whether it could account for failure to achieve the primary outcome at $p<0.05$ was examined. The prognostic significance of early discontinuations due to abdominal pain and/or dyspepsia across all treatment arms is presented in Figure 8.

Discussion

These analyses present the complete data set of the CLASS trial over the entire treatment period, a median duration of 9 months. The data were compared with 6-month results published in the original CLASS report, in view of concerns that it presented a biased point of view. Analyses confirm that results over the first 6 months of treatment accurately reflect differences in the incidence of GI complications between celecoxib and NSAIDs due to differential drop out rates and potential "informative censoring".

Data from the entire CLASS trial presented here, compared with previously published results at 6 months as well as those presented in the celecoxib package label over 9 months of protocol participation do not differ (12,20). Although celecoxib treatment did not statistically differ from the combined NSAID group by the predefined primary outcome of POB's at any timepoint, the secondary outcome: PUBs, significantly favored celecoxib treatment over the entire trial and at 6 months ($p<0.04$). Accounting for changes in practice and patient expectations, the combined outcome of PUB's did not suffer from an inadequate sample size and/or informed censoring; As PUB's represent the same endpoint predefined as the primary outcome measure in the VIGOR trial, it may be concluded that both rofecoxib and celecoxib administration are associated with a clinically meaningful reduction in symptomatic ulcers and ulcer complications.

Despite these re-analyses, the predefined primary outcome in the CLASS trial POB's, fails to differentiate celecoxib treatment from the combined NSAID groups; subanalyses differentiate it only from ibuprofen, not diclofenac, whether data from the entire trial or 6 months treatment are examined. Yet, these observations are not consistent with published reports that the rate of endoscopically confirmed ulcers with diclofenac administration is similar to other non-selective NSAIDs (21,22). Whether the failure to discriminate the effects of celecoxib from diclofenac is due to the possibility that diclofenac's effects are similar to a selective COX-2 inhibitor (not supported by accumulated endoscopic evidence) or is due to too few patients at risk remaining in that treatment arm as a result of informed censoring as described is unfortunately impossible to determine with this trial. In the second 6 months of the study there were unexpectedly high withdrawal rates for GI symptoms than expected leading to too few patients including those at increased risk remaining in the diclofenac treatment arm to answer the question.

Importantly, the risk for symptomatic ulcers and ulcer complications [PUB's] remained constant with celecoxib treatment at 6 months and over the entire trial. In contrast, the incidence of PUB's in the combined NSAID group was significantly less over the entire CLASS trial than at 6 months, and is inconsistent with published data with nonselective NSAIDs. Importantly, the incidence of PUB's in the combined NSAID group in CLASS does reflect results with naproxen treatment in the VIGOR trial (13).

Although "large simple trials" were designed to confirm an improved GI safety profile, suggested in short term endoscopy studies, it is clear they are not "simple". Results from the CLASS trial illustrate that design and execution of a RCT may fail due to changes in clinical practice; use of CV doses of ASA; expectations on the part of patients and physicians leading to early treatment discontinuations, and accrual of a patient population with less risk factors than expected, in part because the test agent was now available by prescription. (23,24)

Conclusions

Analysis of the complete data set of the CLASS trial over the entire treatment period, a median of 9 months, confirmed published results at 6 months. Although it failed to demonstrate statistical significance for celecoxib compared with combined NSAIDs by the primary outcome measure of POBs, the secondary combined outcome of PUBs statistically favored celecoxib over the entire trial and at 6 months. Analyses presented indicate this failure predominantly due to three flaws in trial design: (1) the study was underpowered because fewer patients with risk factors for GI events were recruited than expected; and (2) changes in medical practice: more patients were receiving cardiovascular prophylaxis with ASA and (3) expectations: unexpected early withdrawals for GI tolerability issues with diclofenac and lack of efficacy with ibuprofen.

References

1. Simon LS. Actions and toxicity of nonsteroidal anti-inflammatory drugs. Curr Opin Rheumatol. 1996;8:169-175.

2. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med 1999;340:1888-1899.

3. Verburg KM, Maziasz TJ, Weiner E, Loose L, Geis GS, Isakson PC. COX-2-specific inhibitors: definition of a new therapeutic concept. Am J Therap 2001;8:49-64.

4. Xie W, Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci USA 1991;88:2692-2696.

5. Kujubu DA, Fletcher BS, Varnum BC, Lim RW, Herschman HR. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostglandin synthase/cyclooxygenase homologue. J Biol Chem 1991;266:12866-72.

6. O'Banion MK, Sadowski HB, Winn V, Young DA. A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenasse-related protein. J Biol Chem 1991;266:23261-7.

7. Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. J Rheumatol 1997;(suppl 49)24:15-19.

8. Lipsky PE. Role of cyclooxygenase-1 and –2 in health and disease. Am J Orthop 1999;28(Suppl 3):8-12.

9. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet 1999;354:2106-2111.

10. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA 1999;282:1921-1928.

11. Laine L, Harper S, Simon T, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastoduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. Gastroenterol 1999;117:776-83.

12. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis, the CLASS study: a randomized controlled trial. JAMA 2000;284(10):1247-1255.

13. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343;1520-8.

14. Weil J, Colin JD, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding [see comments]. BMJ 1995;310:827-830.

15. Yola M, Lucien A. Evidence of depletion of susceptibles effect in non-experimental pharmacoepidemioological research. J Clin Epidemiol 1994;47:731-737.

16. Scharfstein D, Robins JM, Eddings W, Rotnitzky A Inference in randomized studies of informative censoring and discrete time-to-event endpoints Biometrics 2001; 57: 404-413,

17. Robins JM, Finklestein D Correcting for non-compliance and dependant censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests Biometrics 2000; 56: 779-788

18. Miller RG Jr Survival Analysis John Wiley and Sons New York 1981

19. Mantel N Evaluation of survival data and two new rank order statistics arising in its consideration Cancer Chemo Reports 1966; 50: 163-170

20. www.pdr.net/display.jsp?url=62950540.html/celebrex+capsules

21. Geis GS, Stead H, Wallemark CB, Nicholson PA Prevalence of mucosal lesions in the stomach and duodenum due to chronic use of NSAID in patients with rheumatoid arthritis or osteoarthritis, an interim report on prevention by misoprostol in diclofenac associated lesions J Rheumatol Suppl 1991 28: 11-14

22. Bolten W, Gomes JA, Stead H, Geis GS The gastrointestinal safety and efficacy of the fixed combination of diclofenac and misoprostol in the treatment of osteoarthritis Br J Rheumatol 1992 31: 753-758

23. Goldstein JL, Silverstein FE, Agrawal NM, Hubbard RC, Kaiser J, Maurath CJ, Verburg KM, Geis GS. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. Am J Gastroenterol, 2000; 95(7):1681-1690.

24. Silverstein FD, Graham DY, Senior JR, et al. Misoprostol reduced serious serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241-9.

Table 1. Patient Disposition; Number (%) of Patients			
	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Completed treatment	2054 (51.5)	994 (49.8)	895 (45.1)
Withdrawn	1933 (48.5)	1002 (50.2)	1090 (54.9)
Reasons for Withdrawal			
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Pre-existing Violation	27 (0.7)	11 (0.6)	11 (0.6)
Protocol Noncompliance	446 (11.2)	177 (8.9)	254 (12.8)
Treatment Failure	617 (15.5)	296 (14.8)	403 (20.3)
Adverse Event	843 (21.1)	518 (26.0)	422 (21.3)

Table 2. Percent of Patients with Risk Factors			
A priori protocol estimate	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
≥75 years (~ 15%)	12.2	11.8	10.9
Hx GI Bleed (~ 3%)	1.7	1.5	1.4
Hx of Ulcer (~ 15%)	8.4	8.5	7.6
Hx of CV Disease (~ 55%)	40.2	40.3	40.0
ASA Use (~ 12%)	21.0	22.0	19.0

Figure Legends

Figure 1: *Incidence of Ulcer Complications (POB's) over the entire CLASS trial and at 6 months with (top panel) and without (bottom panel) concomitant ASA therapy*

The incidence of POB's with celecoxib treatment over the entire trial and at 6 months are 0.73 vs. 0.76 events per 100 patient years, respectively (p=NS). In comparison, the incidence of POB's after 6 months treatment in the combined NSAID group, 1.45 events per 100 patient years decreased to 0.95 events per 100 patient years over the entire trial (p=0.016). The ITT population is presented in the top panel and patients not receiving ASA in the bottom panel.

Figure 2: *Time to Ulcer Complications (POB's) over the entire trial and at 6 months*

In the Kaplan-Meier time to event curve, ITT population (2a) accrual of new GI adverse events slows markedly after 125 days in the NSAID treatment groups but continues through 10 months in the celecoxib treatment arm. In patients not receiving ASA (2b), the incidence of POB's was less than expected, and no events were evident with diclofenac treatment after approximately 60 days of exposure..

Figure 3: *Incidence of Ulcer Complications and Symptomatic Ulcers (PUB's) over the entire trial and at 6 months*

The incidence of PUBs with celecoxib treatment remains constant over the entire trial and at 6 months in the ITT population (3a) and those not receiving ASA (3b). A reduced incidence of PUBS over the entire trial is evident with combined NSAID administration over the entire trial, compared with 6 months

Figure 4: *Incidence of Early Protocol Discontinuation By Cause and Treatment Duration Patients Receiving Celecoxib (top panel), Diclofenac (middle panel) and Ibuprofen (bottom panel).*

Patients randomized to celecoxib treatment continued protocol participation over a longer period of time than either NSAID comparator groups.

Figure 5: *Time to First Patient Report of Mild/Moderate/Severe Abdominal Pain and Treatment Discontinuation (5a); Report of Severe Abdominal Pain and Treatment Discontinuation. (5b).*

The majority of patients discontinued protocol participation within 2.5 weeks of onset of abdominal pain (5a); more evident when these symptoms are reported to be severe. In panel B the x-axis represents the last dosing day, or the treatment discontinuation date while the y axis is the day of onset of symptoms, date of occurrence of abdominal pain. The 45-degree line suggests there was significant correlation between onset of symptoms and the last dose of medication.

Figure 6: *Time to First Patient Report of Mild/Moderate/Severe Dyspepsia and Treatment Discontinuation (6a)*

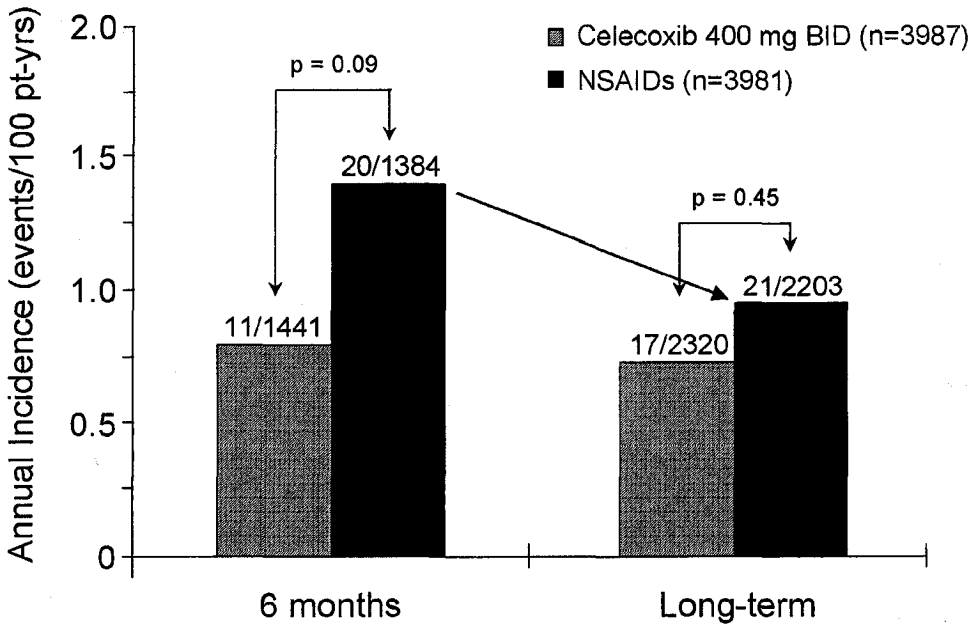
Report of Severe Dyspepsia and Treatment Discontinuation. (6b).

The majority of patients discontinued protocol participation within 2.5 weeks of onset of dyspepsia (top panel); more evident when these symptoms are reported to be severe. In 6b the x-axis represents the last doing day or the treatment discontinuation date while the y axis is the day of onset of symptoms in this context it is the date of occurrence of severe abdominal pain. The 45-degree line suggests there was significant correlation between onset of symptoms and the last dose of medication.

Figure 7: *Comparison of Early Treatment Discontinuations in Patients with or without Abdominal Pain Over Time*. [mild, moderate, severe combined]

Patients continued protocol treatment for a longer period of time in the absence of abdominal pain (solid line) than when reporting this GI adverse event (dashed line). In these data the y-axis represents the proportion of patients not failing and the x-axis represent the days.

Figure 1


Annual Incidence (events/100 pt-yrs)
2.0
1.5
1.0
0.5
0
Celecoxib 400 mg BID (n=3987)
NSAIDs (n=3981)
p = 0.09
p = 0.45
20/1384
11/1441
21/2203
17/2320
6 months
Long-term

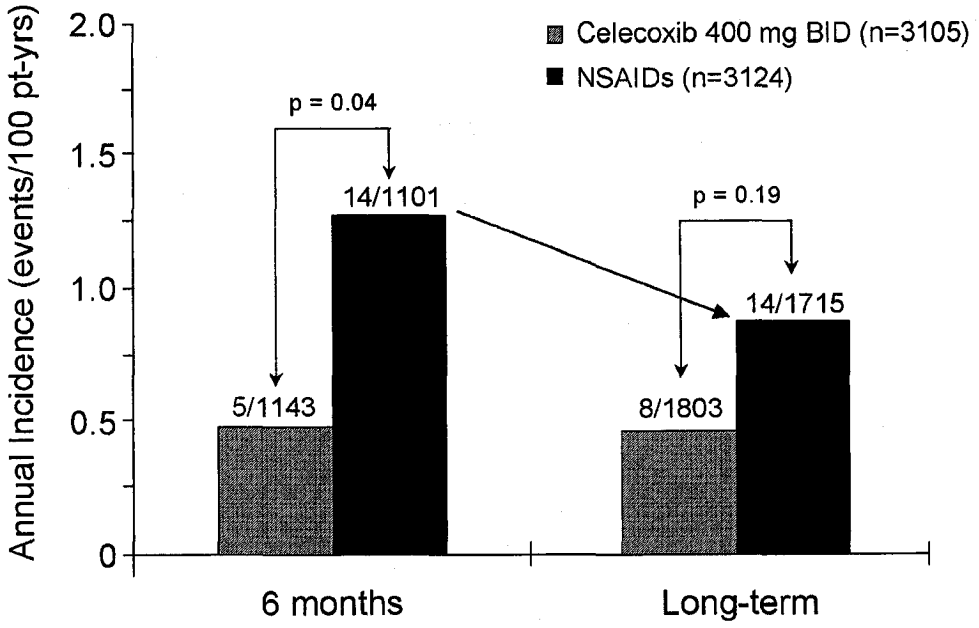

Annual Incidence (events/100 pt-yrs)
2.0
1.5
1.0
0.5
0
Celecoxib 400 mg BID (n=3105)
NSAIDs (n=3124)
p = 0.04
p = 0.19
14/1101
5/1143
14/1715
8/1803
6 months
Long-term

Figure 2A

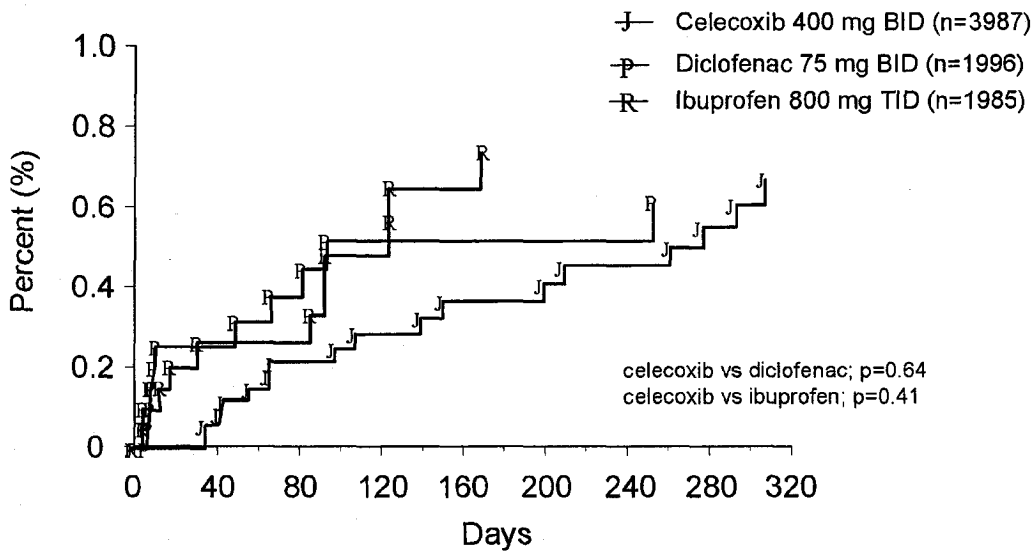

J Celecoxib 400 mg BID (n=3987)
P Diclofenac 75 mg BID (n=1996)
R Ibuprofen 800 mg TID (n=1985)
Percent (%)
1.0
0.8
0.6
0.4
0.2
0
0
40
80
120
160
200
240
280
320
Days
celecoxib vs diclofenac; p=0.64
celecoxib vs ibuprofen; p=0.41

Figure 2 B

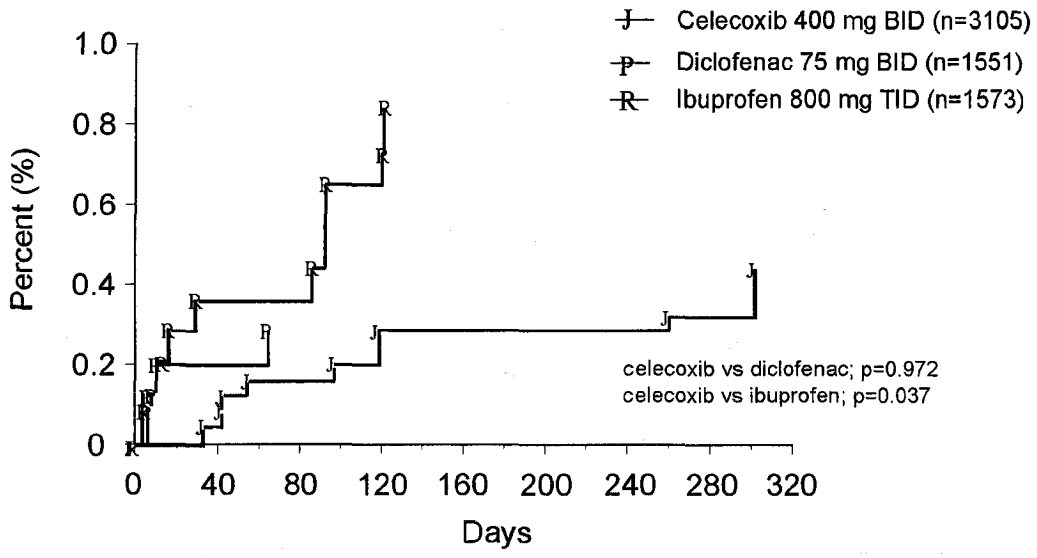

Celecoxib 400 mg BID (n=3105)
Diclofenac 75 mg BID (n=1551)
Ibuprofen 800 mg TID (n=1573)
Percent (%)
1.0
0.8
0.6
0.4
0.2
0
0
40
80
120
160
200
240
280
320
Days
celecoxib vs diclofenac; p=0.972
celecoxib vs ibuprofen; p=0.037

Figure 3 A

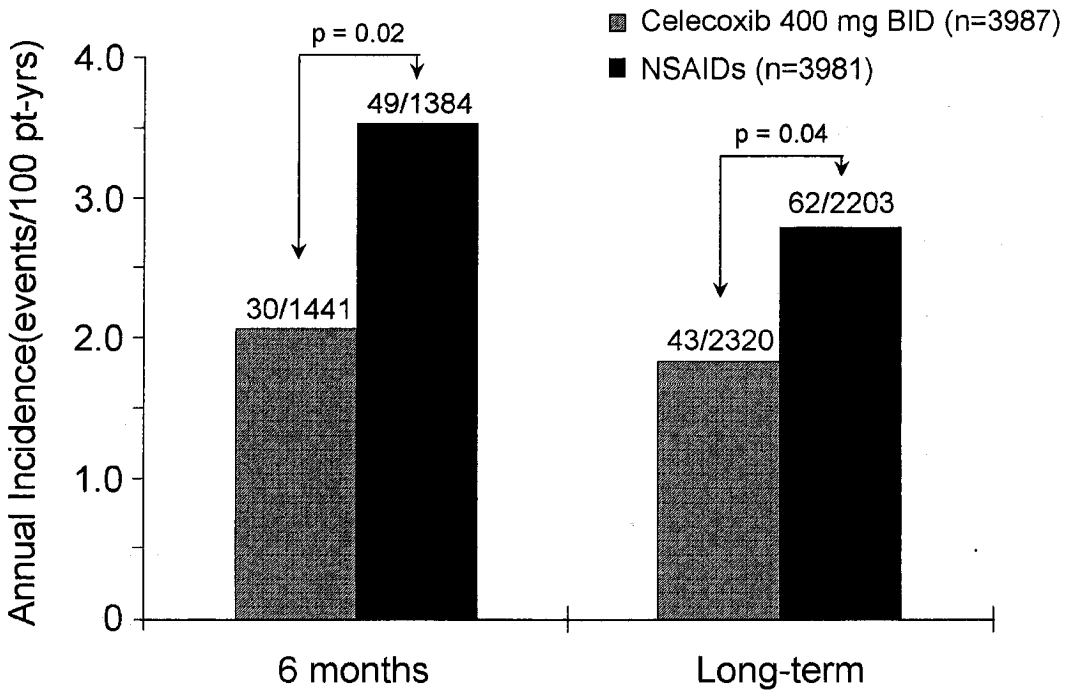

Celecoxib 400 mg BID (n=3987)
NSAIDs (n=3981)
Annual Incidence(events/100 pt-yrs)
4.0
3.0
2.0
1.0
0
p = 0.02
49/1384
30/1441
p = 0.04
62/2203
43/2320
6 months
Long-term

Figure 3 B

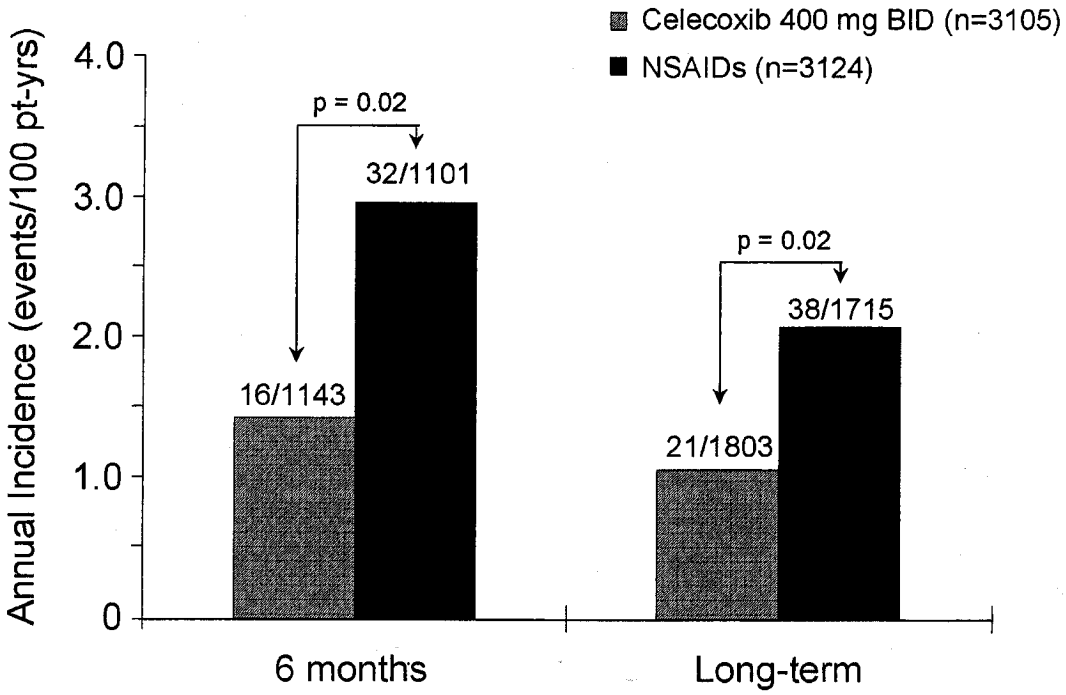
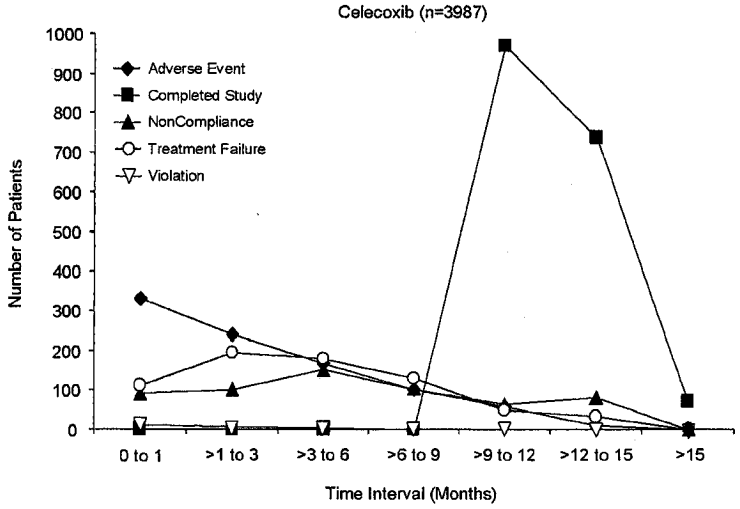
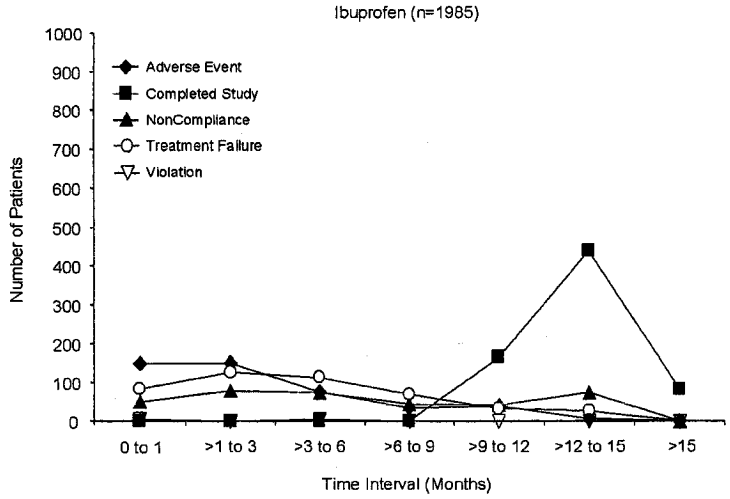

Celecoxib 400 mg BID (n=3105)
NSAIDs (n=3124)
Annual Incidence (events/100 pt-yrs)
4.0
3.0
2.0
1.0
0
p = 0.02
32/1101
16/1143
p = 0.02
38/1715
21/1803
6 months
Long-term

Figure 4


Celecoxib (n=3987)
Adverse Event
Completed Study
NonCompliance
Treatment Failure
Violation
Number of Patients
1000
900
800
700
600
500
400
300
200
100
0
0 to 1
>1 to 3
>3 to 6
>6 to 9
>9 to 12
>12 to 15
>15
Time Interval (Months)


Ibuprofen (n=1985)
Adverse Event
Completed Study
NonCompliance
Treatment Failure
Violation
Number of Patients
1000
900
800
700
600
500
400
300
200
100
0
0 to 1
>1 to 3
>3 to 6
>6 to 9
>9 to 12
>12 to 15
>15
Time Interval (Months)

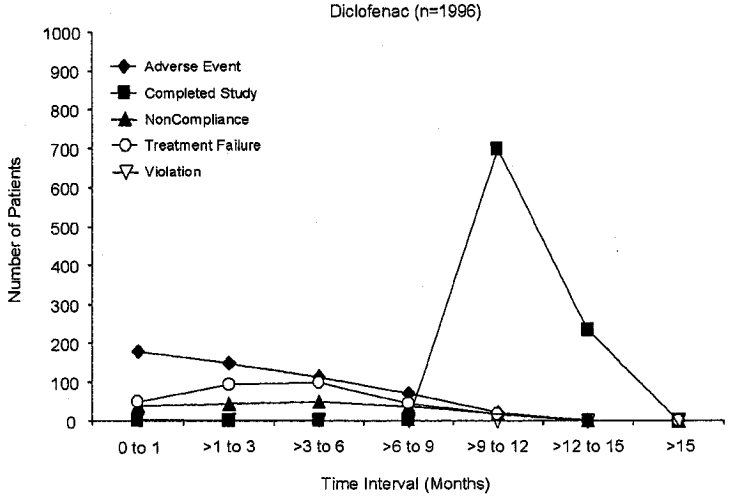
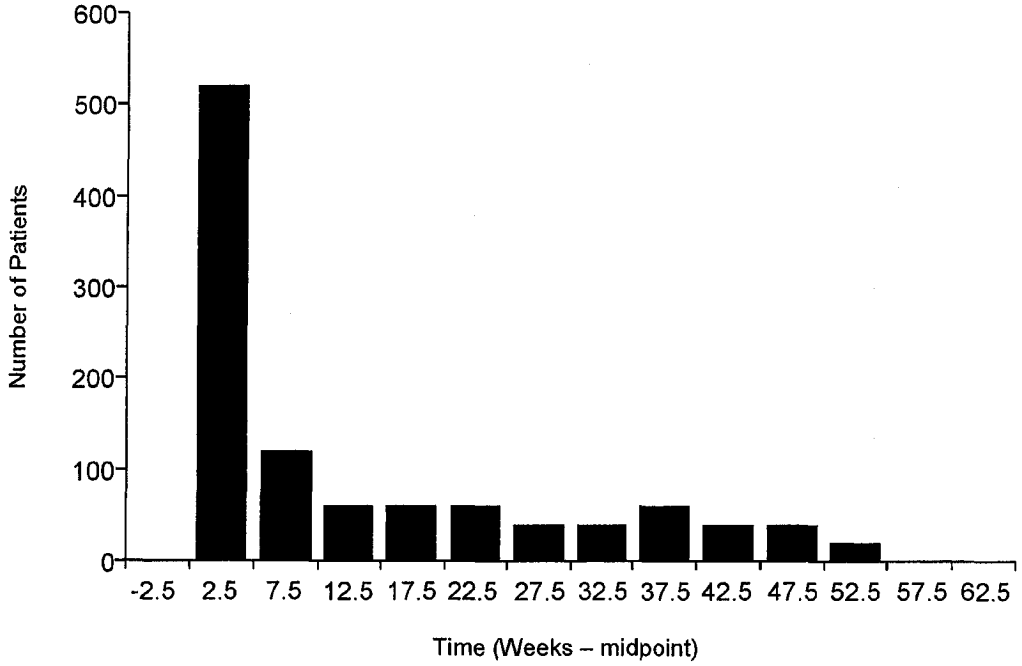

Diclofenac (n=1996)
Adverse Event
Completed Study
NonCompliance
Treatment Failure
Violation
Number of Patients
1000
900
800
700
600
500
400
300
200
100
0
0 to 1
>1 to 3
>3 to 6
>6 to 9
>9 to 12
>12 to 15
>15
Time Interval (Months)

Figure 5a



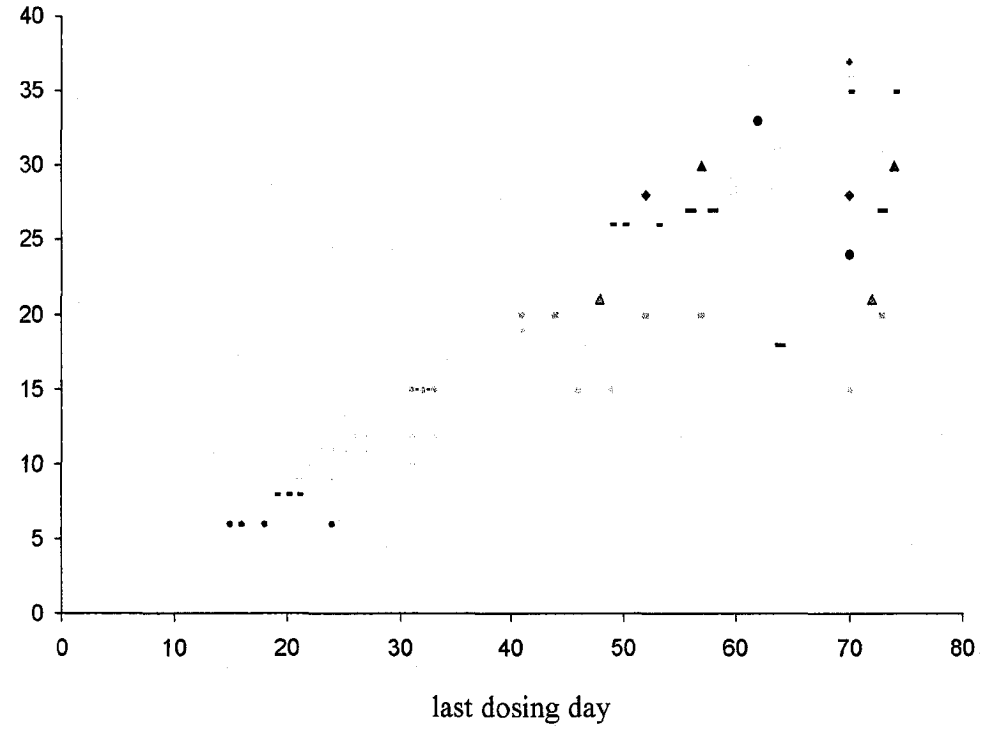
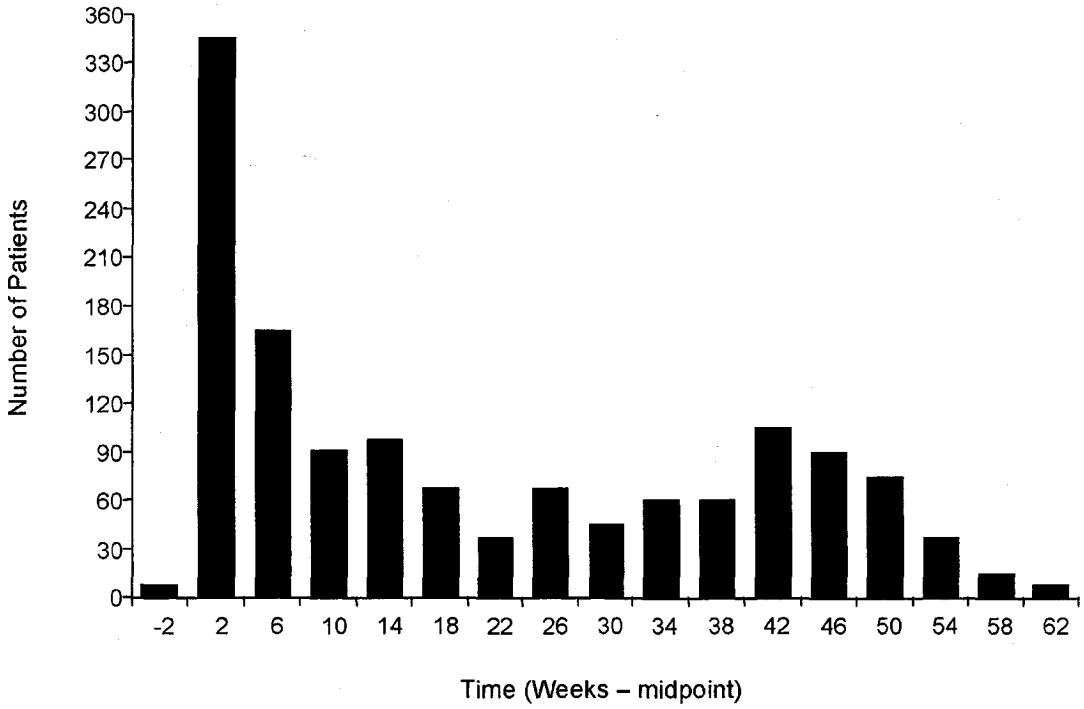


Figure 5b

Figure 6a


Number of Patients
360
330
300
270
240
210
180
150
120
90
60
30
0
-2
2
6
10
14
18
22
26
30
34
38
42
46
50
54
58
62
Time (Weeks – midpoint)

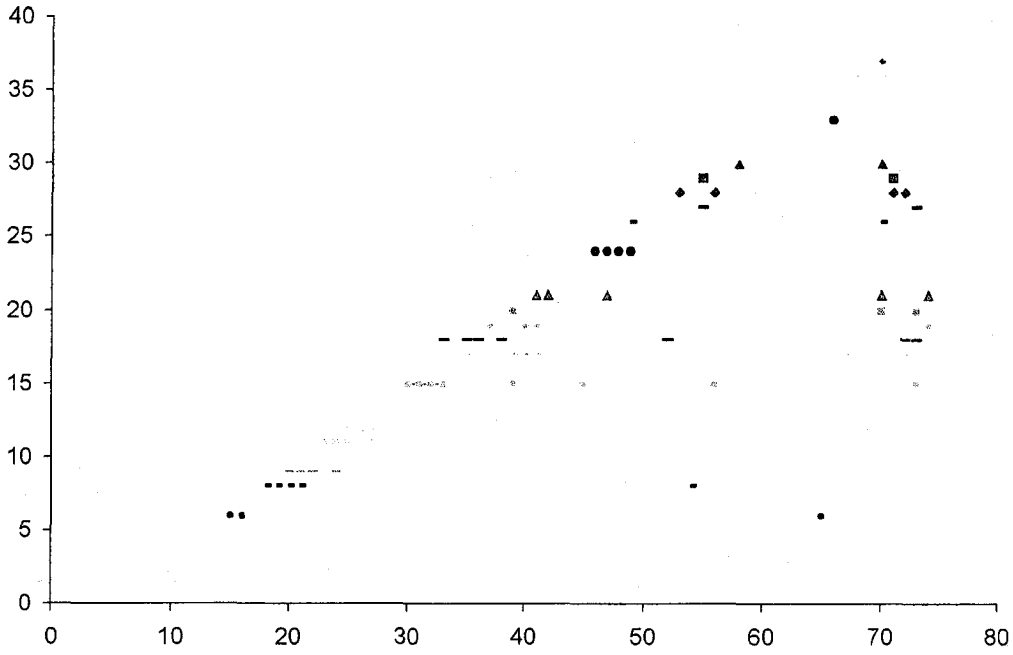


Figure 6b

Figure 7

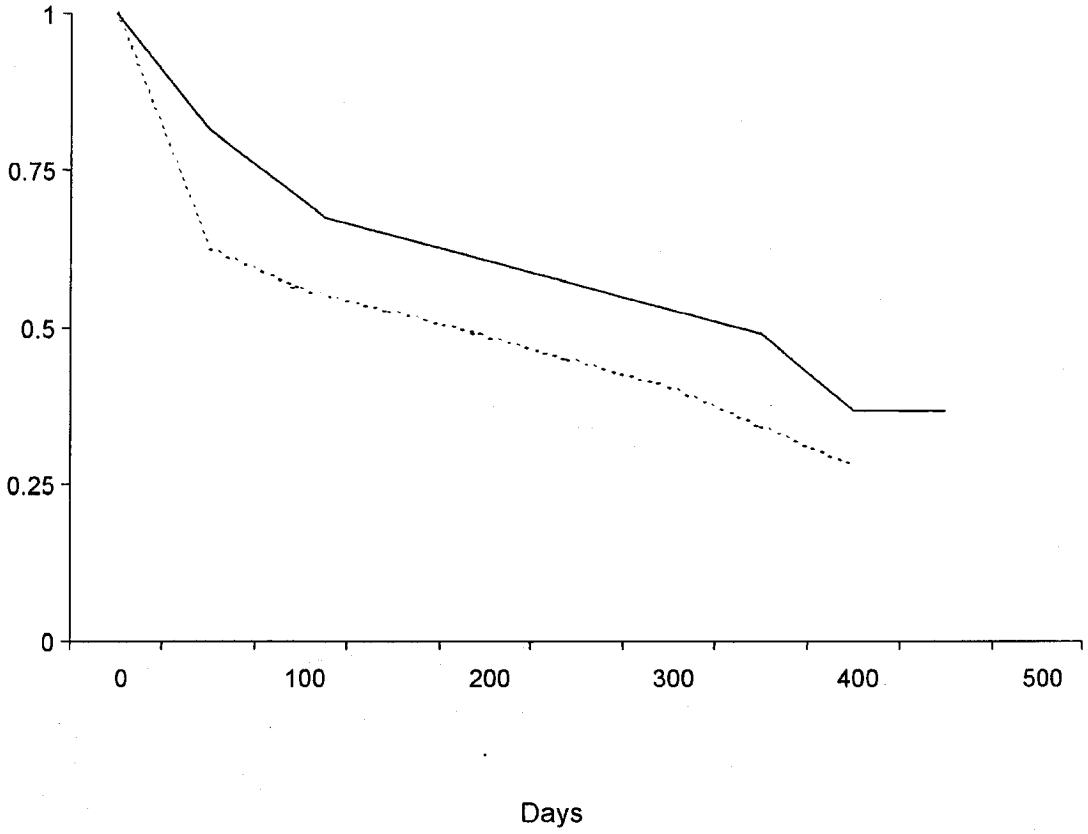


EXHIBIT 177

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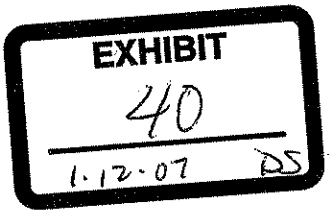

Update on *JAMA*'s Conflict of Interest Policy

Annette Flanagin, RN, MA
Phil B. Fontanarosa, MD, MBA
Catherine D. DeAngelis, MD, MPH

SINCE THE MID-1980S, *JAMA* AND OTHER MEDICAL JOURNALS have encouraged authors to disclose conflicts of interest that they may have in the subject matter of their manuscripts.[1] In 1989, *JAMA* began requiring authors to sign a statement declaring all potential financial conflicts of interest and began including all such disclosures in published articles.[2] Since that time, the journal's conflict of interest policy has continued to evolve with the goal of improving disclosures and transparency for all involved.[3,4] For example, the policy applies to all types of manuscripts, including letters and book reviews, and to all individuals involved in the review, editorial evaluation, and publication process, including peer reviewers, editorial board members, and editors. Most recently, *JAMA* began requiring authors to specifically indicate if they have no conflicts of interest in the subject matter of their manuscript.[4] The International Committee of Medical Journal Editors (ICMJE),[5] the Council of Science Editors (CSE),[6] and the World Association of Medical Editors (WAME)[7] have similar policies.

However, biomedical journals have a wide range of conflict of interest policies (eg, some request disclosures, some require disclosures, and some publish disclosures and some do not).[8,9] Journals also define *relevant* conflicts of interest in different terms to include financial and nonfinancial conflicts or only financial interests, and for financial interests, may define relevance in different monetary amounts or lengths of time. Perhaps because of these different policies, some authors may not fully understand *JAMA*'s requirements for reporting potential conflicts of interest and might not fully disclose their conflicts of interest to *JAMA* at the time they submit their manuscripts. For example, some authors completely disclose all relevant conflicts of interest in the submitted manuscript, whereas other authors disclose relevant interests in a cover letter or only in the authorship form. The result is an inconsistent approach whereby for some authors, the disclosure is completely transparent to all involved in the manuscript evaluation process, including peer reviewers; but for other authors, the disclosure is made public only at the time of publication. In addition, some authors continue to misunderstand what is expected and provide inaccurate or incomplete disclosures that are discovered after publication and result in a published correction or letter of explanation.[10-14]

To further improve the transparency of reporting of potential conflicts of interest and to encourage more accurate and complete disclosures, an important new policy is that *JAMA* will begin requiring all authors to disclose all potential conflicts of interest in the Acknowledgment section of the manuscript at the time of submission. This includes specific financial interests and relationships and affiliations relevant to the subject of the manuscript. Between now and the end of 2006, *JAMA* will permit submissions of manuscripts in which authors' conflict of interest information is not yet included in the manuscript, but with the understanding that this information will be obtained and submitted promptly—and definitely before any revisions are considered. Beginning January 2007, *JAMA* will require that complete disclosures of conflicts of interest from all authors, including declaration of no conflicts of interest, are included in the Acknowledgment section of the manuscript. *JAMA*'s Web-based manuscript submission system will require the corresponding author to indicate that this information is included in the manuscript at the time of submission. Authors will continue to complete and sign an authorship responsibility form that includes statements on conflict of interest as well as funding and support.

Conflicts of interest in biomedical science continue to be under intense and increasing scrutiny. To help ensure transparency and complete reporting of this information, *JAMA*'s policies on conflicts of interest have been updated (as noted below).[15] All authors are encouraged to read these policies carefully and to follow them completely. By doing so, peer reviewers and editors can expect full disclosure of potential conflicts of interest in manuscripts submitted to *JAMA*, and physicians, other health care professionals, and the public can expect complete reporting of conflict of interest information in articles published in *JAMA*.

Author Affiliations: Ms Flanagin (annette.flanagin@jama-archives.org) is Managing Deputy Editor, Dr Fontanarosa is Executive Deputy Editor, and Dr DeAngelis is Editor in Chief, *JAMA*.

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JAMA Conflict of Interest Policy

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Authors also are required to report detailed information regarding all financial and material support for the research and work, including but not limited to grant support, funding sources, and provision of equipment and supplies in the Acknowledgment section of the manuscript.

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Financial Disclosures: None reported.

REFERENCES

1. Lundberg GD, Flanagin A. New requirements for authors: signed statements of authorship responsibility and financial disclosure. *JAMA*. 1989;262:2003-2004.
2. Rennie D, Flanagin A, Glass RM. Conflicts of interest in the publication of science. *JAMA*. 1991;266:266-267.
3. DeAngelis CD, Fontanarosa PB, Flanagin A. Reporting financial conflicts of interest and relationships between investigators and research sponsors. *JAMA*. 2001; 286:89-91.
4. Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting conflicts of interest, financial aspects of research, and role of sponsors in funded studies. *JAMA*. 2005; 294:110-111.
5. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: updated October 2005. http://www.icmje.org. Accessibility verified June 15, 2006.
6. Council of Science Editors. Conflicts of interest and the peer review process. http://www.councilscienceeditors.org/services/draft_approved.cfm. Accessibility verified June 15, 2006.
7. World Association of Medical Editors. WAME recommendations on publication ethics policies for medical journals. http://www.wame.org/pubethicrecom.htm. Accessibility verified June 15, 2006.
8. Krimsky S, Rothenberg LS. Conflict of interest policies in science and medical journals: editorial practices and author disclosures. *Sci Eng Ethics*. 2001;7:205-218.
9. Ancker J, Flanagin A. A comparison of conflict of interest policies at peer-reviewed journals in multiple scientific disciplines. Paper presented at: The Fifth International Congress on Peer Review and Biomedical Publication; September 17, 2005; Chicago, Ill. http://www.ama-assn.org/public/peer/program.html. Accessed June 13, 2006.
10. Incorrect statements on funding/support and role of the sponsors and incorrect and incomplete financial disclosures [published correction online May 16, 2006]. *JAMA*. 2006;295:2482. http://jama.ama-assn.org/cgi/content/full/295/21/2482-c. Accessed June 13, 2006.
11. Ridker PM. Incomplete financial disclosure for study of funding and outcomes in major cardiovascular trials [letter]. *JAMA*. 2006;295:2725-2726.
12. Incomplete financial disclosure [correction]. *JAMA*. 2006;295:2726.
13. Cohen LS, Nonacs R, Viguera AC, et al. Antidepressant treatment and relapse of depression during pregnancy [letter]. *JAMA*. 2006;296:165-167.
14. Incomplete financial disclosure [correction]. *JAMA*. 2006;296:170.
15. Instructions for authors. *JAMA*. 2006;296:107-116.

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EXHIBIT 178

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CELEBREX safely and effectively. See full prescribing information for CELEBREX.

CELEBREX® (celecoxib) capsules
Initial U.S. Approval: 1998

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS
See full prescribing information for complete boxed warning

Cardiovascular Risk

- **CELEBREX, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. *(5.1,14.7)***
- **CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. *(4, 5.1)***

Gastrointestinal Risk

- **NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events. *(5.4)***

----------INDICATIONS AND USAGE----------

CELEBREX is a nonsteroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Acute Pain (AP) (1.5)
- Primary Dysmenorrhea (PD) (1.6)
- Familial Adenomatous Polyposis (FAP)-adjunct to usual care) (1.7)

----------DOSAGE AND ADMINISTRATION----------

Use lowest effective dose for the shortest duration consistent with treatment goals for the individual patient. (1, 5.1, 5.4)

- OA: 200 mg once daily or 100 mg twice daily (2.1, 14.1)
- RA: 100 to 200 mg twice daily (2.2, 14.2)
- JRA: 50 mg twice daily in patients 10-25 kg. 100 mg twice daily in patients more than 25 kg (2.3, 14.3)
- AS: 200 mg once daily single dose or 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit (2.4, 14.4)
- AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On subsequent days, 200 mg twice daily as needed (2.5, 14.5)
- FAP: 400 mg twice daily with food, as an adjunct to usual care (2.6, 14.6)

Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B).

Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers, (2.7, 8.4, 8.8, 12.3).

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 50 mg, 100 mg, 200 mg and 400 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to celecoxib or sulfonamides (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4, 5.7, 5.8, 5.13)
- Use during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)

----------WARNINGS AND PRECAUTIONS----------

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Patients with known CV disease/risk factors may be at greater risk (5.1, 14.7, 17.2).
- Serious gastrointestinal (GI) adverse events, which can be fatal. The risk is greater in patients with a prior history of ulcer disease or GI bleeding, and in patients at high risk for GI events, especially the elderly. CELEBREX should be used with caution in these patients (5.4, 8.5, 14.7, 17.3).
- Elevated liver enzymes and, rarely, severe hepatic reactions. Discontinue use of CELEBREX immediately if abnormal liver enzymes persist or worsen (5.5, 17.4).
- New onset or worsening of hypertension. Blood pressure should be monitored closely during treatment with CELEBREX (5.2, 7.4, 17.2).
- Fluid retention and edema. CELEBREX should be used with caution in patients with fluid retention or heart failure (5.3, 17.6).
- Renal papillary necrosis and other renal injury with long term use. Use CELEBREX with caution in the elderly, those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics, ACE-inhibitors, or angiotensin II antagonists (5.6, 7.4, 8.7, 17.6).
- Anaphylactoid reactions. Do not use CELEBREX in patients with the aspirin triad (5.7, 10, 17.7).
- Serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal and can occur without warning even without known prior sulfa allergy. Discontinue CELEBREX at first appearance of rash or skin reactions (5.8, 17.5).

----------ADVERSE REACTIONS----------

Most common adverse reactions in arthritis trials (>2% and >placebo): abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Concomitant use of CELEBREX and warfarin may result in increased risk of bleeding complications. (7.1)
- Concomitant use of CELEBREX increases lithium plasma levels. (7.2)
- Concomitant use of CELEBREX may reduce the antihypertensive effect of ACE Inhibitors and angiotensin II antaonists (7.4)
- Use caution with drugs known to inhibit P450 2C9 or metabolized by 2D6 due to the potential for increased plasma levels (2.7, 8.4, 8.8, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation (5.9, 8.1, 17.8)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: June 2009

EXHIBIT
60
DENISE D. BACH 7/27/10

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

Cardiovascular Risk

- **CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All nonsteroidal anti-inflammatory drugs (NSAIDs) may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.** ***(5.1,14.7)***
- **CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.** ***(4, 5.1)***

Gastrointestinal Risk

- **NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.** ***(5.4)***

1. INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*]

1.1 Osteoarthritis (OA)

CELEBREX is indicated for relief of the signs and symptoms of OA [*see Clinical Studies (14.1)*]

1.2 Rheumatoid Arthritis (RA)

CELEBREX is indicated for relief of the signs and symptoms of RA [*see Clinical Studies (14.2)*]

1.3 Juvenile Rheumatoid Arthritis (JRA)

CELEBREX is indicated for relief of the signs and symptoms of JRA in patients 2 years and older [*see Clinical Studies (14.3)*]

1.4 Ankylosing Spondylitis (AS)

CELEBREX is indicated for the relief of signs and symptoms of AS [*see Clinical Studies (14.4)*]

1.5 Acute Pain (AP)

CELEBREX is indicated for the management of AP in adults [*see Clinical Studies (14.5)*]

1.6 Primary Dysmenorrhea (PD)

CELEBREX is indicated for the treatment of PD [*see Clinical Studies (14.5)*]

1.7 Familial Adenomatous Polyposis (FAP)

CELEBREX is indicated to reduce the number of adenomatous colorectal polyps in FAP, as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of CELEBREX treatment will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX treatment in patients with FAP beyond six months have not been studied [*see Warnings and Precautions (5.15), Clinical Studies (14.6)*]

2. DOSAGE AND ADMINISTRATION

Use lowest effective dose for the shortest duration consistent with treatment goals for the individual patient.

These doses can be given without regard to timing of meals.

2.1 Osteoarthritis

For relief of the signs and symptoms of OA the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice daily.

2.2 Rheumatoid Arthritis

For relief of the signs and symptoms of RA the recommended oral dose is 100 to 200 mg twice daily.

2.3 Juvenile Rheumatoid Arthritis

For the relief of the signs and symptoms of JRA the recommended oral dose for pediatric patients (age 2 years and older) is based on weight. For patients ≥10 kg to ≤25 kg the recommended dose is 50 mg twice daily. For patients >25 kg the recommended dose is 100 mg twice daily.

For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F).

2.4 Ankylosing Spondylitis

For the management of the signs and symptoms of AS, the recommended dose of CELEBREX is 200 mg daily in single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

2.5 Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of CELEBREX is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

2.6 Familial Adenomatous Polyposis

Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg twice per day to be taken with food.

2.7 Special Populations

Hepatic insufficiency: The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [*see Warnings and Precautions (5.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Poor Metabolizers of CYP2C9 Substrates: Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers. Consider using alternative management in JRA patients who are poor metabolizers. [*see Use in Specific populations (8.8), and Clinical Pharmacology (12.3)*].

3. DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 100 mg, 200 mg and 400 mg

4. CONTRAINDICATIONS

CELEBREX is contraindicated:

- In patients with known hypersensitivity to celecoxib, aspirin, or other NSAIDs.
- In patients who have demonstrated allergic-type reactions to sulfonamides.
- In patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe anaphylactoid reactions to NSAIDs, some of them fatal, have been reported in such patients [*see Warnings and Precautions (5.7, 5.13)*].
- For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*].

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Chronic use of CELEBREX may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. In the APC (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with CELEBREX 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [*see Clinical Studies (14.7)*].

All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with CELEBREX, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and CELEBREX does increase the risk of serious GI events [*see Warnings and Precautions (5.4)*].

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [*see Contraindications (4)*].

5.2 Hypertension

As with all NSAIDs, CELEBREX can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including CELEBREX, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with CELEBREX and throughout the course of therapy. The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively [*see Clinical Studies (14.7)*].

5.3 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs, including CELEBREX [*see Adverse Reactions (6.1)*]. In the CLASS study [*see Clinical Studies (14.7)*], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. CELEBREX should be used with caution in patients with fluid retention or heart failure.

5.4 Gastrointestinal (GI) Effects

Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including CELEBREX, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [*see Clinical Studies (14.7)*]. With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during CELEBREX therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

5.5 Hepatic Effects

Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX [*see Adverse Reactions (6.1)*]. In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

5.6 Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced renal disease. Therefore, treatment with CELEBREX is not

recommended in these patients with advanced renal disease. If CELEBREX therapy must be initiated, close monitoring of the patient's renal function is advisable.

5.7 Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [*see Contraindications (4), Warnings and Precautions (5.7)*]. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

5.8 Skin Reactions

CELEBREX is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy

In late pregnancy, starting at 30 weeks gestation, CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus [*see Use in Specific Populations (8.1)*].

5.10 Corticosteroid Treatment

CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

5.11 Hematological Effects

Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages [*see Clinical Pharmacology (12.2)*].

5.12 Disseminated Intravascular Coagulation (DIC)

CELEBREX should be used only with caution in pediatric patients with systemic onset JRA due to the risk of disseminated intravascular coagulation.

5.13 Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

5.14 Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, CELEBREX should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.15 GI Cancer in Familial Adenomatous Polyposis

Treatment with CELEBREX in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of CELEBREX. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

5.16 Inflammation

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

5.17 Concomitant NSAID Use

The concomitant use of CELEBREX with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

6. ADVERSE REACTIONS

Of the CELEBREX-treated patients in the pre-marketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of CELEBREX of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Pre-marketing Controlled Arthritis Trials

Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 1: Adverse Events Occurring in ≥2% of CELEBREX Patients from Pre-marketing Controlled Arthritis Trials

	CBX N=4146	Placebo N=1864	NAP N=1366	DCF N=387	IBU N=345
Gastrointestinal					
Abdominal Pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral Edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-Accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central, Peripheral Nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis					
Rhinitis	2.3%	1.1%	1.7%	1.6%	2.6%
Sinusitis	2.0%	1.3%	2.4%	2.3%	0.6%
Upper Respiratory	5.0%	4.3%	4.0%	5.4%	5.8%
Infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

CBX = CELEBREX 100 – 200 mg twice daily or 200 mg once daily;
NAP = Naproxen 500 mg twice daily;
DCF = Diclofenac 75 mg twice daily;
IBU = Ibuprofen 800 mg three times daily.

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse reactions occurred in 0.1 - 1.9% of patients treated with CELEBREX (100 - 200 mg twice daily or 200 mg once daily):

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General: Allergy aggravated, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, paresthesia, vertigo

Hearing and vestibular: Deafness, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary: Hepatic function abnormal, SGOT increased, SGPT increased

Metabolic and nutritional: BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

Musculoskeletal: Arthralgia, arthrosis, myalgia, synovitis, tendinitis

Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia,

Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

Hemic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia

Skin and appendages: Alopecia, dermatitis, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders: Cellulitis, dermatitis contact

Urinary: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following serious adverse events (causality not evaluated) occurred in <0.1% of patients (cases reported only in post-marketing experience are indicated *in italics*):

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis, deep venous thrombosis*

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

Liver and biliary: Cholelithiasis, *hepatitis, jaundice, liver failure*

Hemic and lymphatic: Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leucopenia*

Metabolic: *Hypoglycemia, hyponatremia*

Nervous: Ataxia, suicide, *aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage [see Drug Interactions (7.1)]*

Renal: Acute renal failure, *interstitial nephritis*

Skin: *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*

General: Sepsis, sudden death, *anaphylactoid reaction, angioedema*

6.2 The Celecoxib Long-Term Arthritis Safety Study [see *Special Studies* (14.7)]

Hematological Events: The incidence of clinically significant decreases in hemoglobin (>2 g/dL) was lower in patients on CELEBREX 400 mg twice daily (0.5%) compared to patients on either diclofenac 75 mg twice daily (1.3%) or ibuprofen 800 mg three times daily 1.9%. The lower incidence of events with CELEBREX was maintained with or without ASA use [*see Clinical Pharmacology (12.2)*].

Withdrawals/Serious Adverse Events: Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for CELEBREX, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e., causing hospitalization or felt to be life-threatening or otherwise medically significant), regardless of causality, were not different across treatment groups (8%, 7%, and 8%, respectively).

6.3 Juvenile Rheumatoid Arthritis Study

In a 12-week, double-blind, active-controlled study, 242 JRA patients 2 years to 17 years of age were treated with celecoxib or naproxen; 77 JRA patients were treated with celecoxib 3 mg/kg BID, 82 patients were treated with celecoxib 6 mg/kg BID, and 83 patients were treated with naproxen 7.5 mg/kg BID. The most commonly occurring (≥5%) adverse events in celecoxib treated patients were headache, fever (pyrexia), upper

abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal pain, and dizziness (Table 2). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg BID had no observable deleterious effect on growth and development during the course of the 12-week double-blind study. There was no substantial difference in the number of clinical exacerbations of uveitis or systemic features of JRA among treatment groups.

In a 12-week, open-label extension of the double-blind study described above, 202 JRA patients were treated with celecoxib 6 mg/kg BID. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

Table 2: Adverse Events Occurring in ≥5% of JRA Patients in Any Treatment Group, by System Organ Class (% of patients with events)

	All Doses Twice Daily		
System Organ Class Preferred Term	**Celecoxib 3 mg/kg N=77**	**Celecoxib 6 mg/kg N=82**	**Naproxen 7.5 mg/kg N=83**
Any Event	**64**	**70**	**72**
Eye Disorders	**5**	**5**	**5**
Gastrointestinal	**26**	**24**	**36**
Abdominal pain NOS	4	7	7
Abdominal pain upper	8	6	10
Vomiting NOS	3	6	11
Diarrhea NOS	5	4	8
Nausea	7	4	11
General	**13**	**11**	**18**
Pyrexia	8	9	11
Infections	**25**	**20**	**27**
Nasopharyngitis	5	6	5
Injury and Poisoning	**4**	**6**	**5**
Investigations*	**3**	**11**	**7**
Musculoskeletal	**8**	**10**	**17**
Arthralgia	3	7	4
Nervous System	**17**	**11**	**21**
Headache NOS	13	10	16
Dizziness (excl vertigo)	1	1	7
Respiratory	**8**	**15**	**15**
Cough	7	7	8
Skin & Subcutaneous	**10**	**7**	**18**

* Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS

6.4 Other Pre-Approval Studies

Adverse Events from Ankylosing Spondylitis Studies: A total of 378 patients were treated with CELEBREX in placebo- and active-controlled AS studies. Doses up to 400 mg once daily were studied. The types of adverse events reported in the AS studies were similar to those reported in the OA/RAstudies.

Adverse Events from Analgesia and Dysmenorrhea Studies: Approximately 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

Adverse Events from the Familial Adenomatous Polyposis Study: The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis-controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg twice daily, and two at 400 mg twice daily) who had prior intestinal surgery.

6.5 The APC and PreSAP Trials

Adverse reactions from long-term, placebo-controlled polyp prevention studies: Exposure to CELEBREX in the APC and PreSAP trials was 400 to 800 mg daily for up to 3 years [*see Special Studies Adenomatous Polyp Prevention Studies (14.7)*].

Some adverse reactions occurred in higher percentages of patients than in the arthritis pre-marketing trials (treatment durations up to 12 weeks; see *Adverse events from* CELEBREX *pre-marketing controlled arthritis trials*, above). The adverse reactions for which these differences in patients treated with CELEBREX were greater as compared to the arthritis pre-marketing trials were as follows:

	CELEBREX (400 to 800 mg daily) N = 2285	**Placebo N=1303**
Diarrhea	10.5%	7.0%
Gastroesophageal reflux disease	4.7%	3.1%
Nausea	6.8%	5.3%
Vomiting	3.2%	2.1%
Dyspnea	2.8%	1.6%
Hypertension	12.5%	9.8%

The following additional adverse reactions occurred in ≥0.1% and <1% of patients taking CELEBREX, at an incidence greater than placebo in the long-term polyp prevention studies and were either not reported during the controlled arthritis pre-marketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

Nervous system disorders: Cerebral infarction

Eye disorders: Vitreous floaters, conjunctival hemorrhage

Ear and labyrinth: Labyrinthitis

Cardiac disorders: Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders: Deep vein thrombosis

Reproductive system and breast disorders: Ovarian cyst

Investigations: Blood potassium increased, blood sodium increased, blood testosterone decreased

Injury, poisoning and procedural complications: Epicondylitis, tendon rupture

7. DRUG INTERACTIONS

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 should be done with caution. Significant interactions may occur when celecoxib is administered together with drugs that inhibit CYP2C9.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a

potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6.

7.1 Warfarin

Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily 2-5 mg doses of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

7.2 Lithium

In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with CELEBREX 200 mg twice daily as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

7.3 Aspirin

CELEBREX can be used with low-dose aspirin. However, concomitant administration of aspirin with CELEBREX increases the rate of GI ulceration or other complications, compared to use of CELEBREX alone [*see Warnings and Precautions (5.1, 5.4) and Clinical Studies (14.7)*]. **Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis [*see Clinical Pharmacology (12.2)*].**

7.4 ACE-inhibitors and Angiotensin II Antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors and angiotensin II antagonists [*see Clinical Pharmacology (12.2*].

7.5 Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole [*see Clinical Pharmacology (12.3)*]. CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

7.6 Furosemide

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

7.7 Methotrexate

In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have an effect on the pharmacokinetics of methotrexate [*see Clinical Pharmacology (12.3)*].

7.8 Concomitant NSAID Use

The concomitant use of CELEBREX with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Pregnancy category D from 30 weeks of gestation onward.

Teratogenic effects: Celecoxib at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg twice daily) throughout organogenesis. There are no studies in pregnant women. CELEBREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg twice daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided.

8.2 Labor and Delivery

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of CELEBREX in breast milk. The calculated average daily infant dose was 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when CELEBREX is administered to a nursing woman.

8.4 Pediatric Use

CELEBREX is approved for relief of the signs and symptoms of Juvenile Rheumatoid Arthritis in patients 2 years and older. Safety and efficacy have not been studied beyond six months in children. The long-term cardiovascular toxicity in children exposed to CELEBREX has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIDs [*(see Boxed Warning, Warnings and Precautions (5.12), and Clinical Studies (14.3)*].

The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12-week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). NSAIDs including celecoxib should be used only with caution in patients with systemic onset JRA, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests [see *Dosage and Administration (2.3), Warnings and Precautions (5.12), Adverse Reactions (6.3), Animal Toxicology (13.2), Clinical Studies (14.3)*].

Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see *Poor Metabolizers of CYP2C9 substrates (8.8)*].

8.5 Geriatric Use

Of the total number of patients who received CELEBREX in pre-approval clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in

effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients [*see Warnings and Precautions (5.4, 5.6)*].

8.6 Hepatic Insufficiency

The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)*].

8.7 Renal Insufficiency

CELEBREX is not recommended in patients with severe renal insufficiency [*see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)*].

8.8 Poor Metabolizers of CYP2C9 Substrates

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)*].

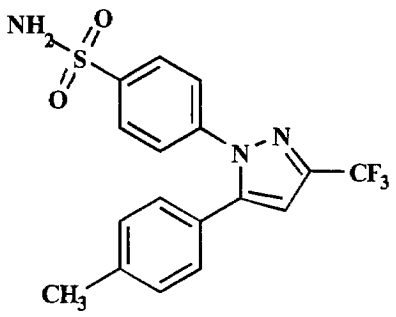
10. OVERDOSAGE

No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

11. DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38; the chemical structure is as follows:



CELEBREX oral capsules contain either 50 mg, 100 mg, 200 mg or 400 mg of celecoxib, together with inactive ingredients including: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CELEBREX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, CELEBREX reduced the incidence and multiplicity of tumors.

12.2 Pharmacodynamics

Platelets: In clinical trials using normal volunteers, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of CELEBREX on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of CELEBREX.

Fluid Retention: Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

12.3 Pharmacokinetics

Absorption: Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose-proportional up to 200 mg BID; at higher doses there are less than proportional increases in C_{max} and AUC *[see Food Effects]*. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5. The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 3.

Table 3
Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
C_{max}, ng/mL	T_{max}, hr	Effective $t_{1/2}$, hr	V_{ss}/F, L	CL/F, L/hr
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1] Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects: When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media.

Coadministration of CELEBREX with an aluminum- and magnesium-containing antacids resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. CELEBREX, at doses up to 200 mg twice daily, can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in Cmax, Tmax or $t_{1/2}$ after administration of capsule contents on applesauce [see *Dosage and Administration (2)*].

Distribution: In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism: Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see *Dosage and Administration (2.7), Use in Specific Populations (8.8)*].

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose [see *Dosage and Administration (2.7) and Use in Specific Populations (8.5)*].

Pediatric: The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 JRA patients 2 years to 17 years of age weighing ≥10 kg with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient.

Twice-daily administration of 50 mg capsules to JRA patients weighing ≥12 to ≤25 kg and 100 mg capsules to JRA patients weighing >25 kg should achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily (*see Dosage and Administration (2.3)*. Celecoxib has not been studied in JRA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks.

Race: Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Insufficiency: A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended [*see Dosage and Administration (2.7) and Use in Specific Populations (8.6)*].

Renal Insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CELEBREX is not recommended in patients with severe renal insufficiency [*see Warnings and Precautions (5.6)*].

Drug interactions:

In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

In vivo studies have shown the following:

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with CELEBREX 200 mg twice daily as compared to subjects receiving lithium alone [*see Drug Interactions (7.2)*].

Fluconazole: Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole [*see Drug Interactions (7.5)*].

Other Drugs: The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate [*see Drug Interactions (7.7)*], phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2-to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg twice daily) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg twice daily based on the AUC_{0-24}).

13.2 Animal Toxicology

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These

reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.

14. CLINICAL STUDIES

14.1 Osteoarthritis

CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.

14.2 Rheumatoid Arthritis

CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg twice daily and 200 mg twice daily were similar in effectiveness and both were comparable to naproxen 500 mg twice daily.

Although CELEBREX 100 mg twice daily and 200 mg twice daily provided similar overall effectiveness, some patients derived additional benefit from the 200 mg twice daily dose. Doses of 400 mg twice daily provided no additional benefit above that seen with 100-200 mg twice daily.

14.3 Juvenile Rheumatoid Arthritis

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients from 2 years to 17 years of age with pauciarticular, polyarticular course JRA or systemic onset JRA (with currently inactive systemic features), received one of the following treatments: celecoxib 3 mg/kg (to a maximum of 150 mg) twice daily; celecoxib 6 mg/kg (to a maximum of 300 mg) twice daily; or naproxen 7.5 mg/kg (to a maximum of 500 mg) twice daily. The response rates were based upon the JRA Definition of Improvement greater than or equal to 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates at week 12 were 69%, 80% and 67% in the celecoxib 3 mg/kg BID, celecoxib 6 mg/kg BID, and naproxen 7.5 mg/kg BID treatment groups, respectively.

The efficacy and safety of CELEBREX for JRA have not been studied beyond six months. The long-term cardiovascular toxicity in children exposed to CELEBREX has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIDs [*see Boxed Warning, Warnings and Precautions (5.12)*].

14.4 Ankylosing Spondylitis

CELEBREX was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. CELEBREX at doses of 100 mg twice daily, 200 mg once daily and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg CELEBREX doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to CELEBREX 400 mg, 53%, than to CELEBREX 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 to 100 mm scale, in at least three of the four following domains: patient global pain, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.

14.5 Analgesia, including Primary Dysmenorrhea

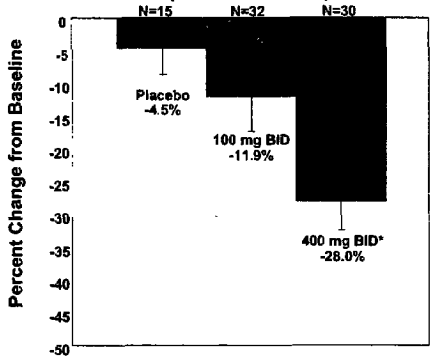
In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses [*see Dosage and Administration (2.5)*] of CELEBREX provided pain relief within 60 minutes.

14.6 Familial Adenomatous Polyposis

CELEBREX was evaluated to reduce the number of adenomatous colorectal polyps. A randomized, double-blind, placebo-controlled study was conducted in patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg twice daily, 12% for CELEBREX 100 mg twice daily and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg twice daily was statistically superior to placebo at the six-month timepoint (p=0.003). (See Figure 1)

Figure 1
Percent Change from Baseline in Number of Colorectal Polyps (FAP Patients)



* p=0.003 versus placebo

14.7 Special Studies

Adenomatous Polyp Prevention Studies:
Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three year studies involving patients with Sporadic Adenomatous Polyps treated with CELEBREX: the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated):

- In the APC trial, the hazard ratios compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.
- In the PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

Clinical trials of other COX-2 selective and non-selective NSAIDs of up to three-years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk.

Celecoxib Long-Term Arthritis Safety Study (CLASS):
This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on CELEBREX and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of complicated ulcers compared to those not on ASA (N=3105). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low-dose ASA and those not on ASA, respectively [*see Warnings and Precautions (5.4)*].

The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with CELEBREX 400 mg twice daily are described in Table 4. Table 4 also displays results for patients less than or greater than 65 years of age. The difference in rates between CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

Table 4: Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors

All Patients	
CELEBREX alone (n=3105)	0.78
CELEBREX with ASA (n=882)	2.19
Patients <65 Years	
CELEBREX alone (n=2025)	0.47
CELEBREX with ASA (n=403)	1.26
Patients ≥65 Years	
CELEBREX alone (n=1080)	1.40
CELEBREX with ASA (n=479)	3.06

In a small number of patients with a history of ulcer disease, the complicated and symptomatic ulcer rates in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the CELEBREX, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for CELEBREX, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree.

Endoscopic Studies: The correlation between findings of short-term endoscopic studies with CELEBREX and the relative incidence of clinically significant serious upper GI events with long-term use has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials [*see Warnings and Precautions (5.4) and Clinical Studies (14.7)*]

A randomized, double-blind study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking CELEBREX 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, CELEBREX was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial [*see Clinical Studies (14.7)*].

The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled studies in 2157 OA and RA patients in whom baseline endoscopies revealed no ulcers. There was no dose relationship for the incidence of gastroduodenal ulcers and the dose of CELEBREX (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice daily was 16.2 and 17.6% in the two studies, for placebo was 2.0 and 2.3%, and for all doses of CELEBREX the incidence ranged between 2.7%-5.9%. There have been no large, clinical outcome studies to compare clinically relevant GI outcomes with CELEBREX and naproxen.

In the endoscopic studies, approximately 11% of patients were taking aspirin (≤ 325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

16. HOW SUPPLIED/STORAGE AND HANDLING
CELEBREX 50 mg capsules are white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body, supplied as:

NDC Number	Size

0025-1515-01	bottle of 60

CELEBREX 100 mg capsules are white, with reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025-1520-31	bottle of 100
0025-1520-51	bottle of 500
0025-1520-34	carton of 100 unit dose

CELEBREX 200 mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025-1525-31	bottle of 100
0025-1525-51	bottle of 500
0025-1525-34	carton of 100 unit dose

CELEBREX 400 mg capsules are white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body, supplied as:

NDC Number	Size
0025-1530-02	bottle of 60
0025-1530-01	carton of 100 unit dose

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

17. PATIENT COUNSELING INFORMATION

Patients should be informed of the following information before initiating therapy with CELEBREX and periodically during the course of ongoing therapy.

17.1 Medication Guide

Patients should be informed of the availability of a Medication Guide for NSAIDs that accompanies each prescription dispensed, and should be instructed to read the Medication Guide prior to using CELEBREX.

17.2 Cardiovascular Effects

Patients should be informed that CELEBREX may cause serious CV side effects such as MI or stroke, which may result in hospitalization and even death. Patients should be informed of the the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and to seek immediate medical advice if they observe any of these signs or symptoms. [*see Warnings and Precautions (5.1)*].

Patients should be informed that CELEBREX can lead to the onset of new hypertension or worsening of preexisting hypertension, and that CELEBREX may impair the response of some antihypertensive agents. Patients should be instructed on the proper follow up for monitoring of blood pressure. [*see Warnings and Precautions (5.2) and Drug Interactions (7.4)*].

17.3 Gastrointestinal Effects

Patients should be informed that CELEBREX can cause gastrointestinal discomfort and more serious side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Patients should be informed of the signs and symptoms of ulcerations and bleeding, and to seek immediate medical advice if they observe any signs or symptoms that are indicative of these disorders, including epigastric pain, dyspepsia, melena, and hematemesis. [*see Warnings and Precautions (5.4)*].

17.4 Hepatic Effects

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms) Patients should be instructed that they should stop therapy and seek immediate medical therapy if these signs and symptoms occur [*see Warnings and Precautions (5.5), Use in Specific Populations (8.6)*].

17.5 Adverse Skin Reactions

Patients should be informed that CELEBREX is a sulfonamide and can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be informed of the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and seek immediate medical advice when observing any indicative signs or symptoms.

Patients should be advised to stop CELEBREX immediately if they develop any type of rash and contact their physician as soon as possible.

Patients with prior history of sulfa allergy should not take CELEBREX [*see Warnings and Precautions (5.8)*].

17.6 Weight Gain and Edema

Long-term administration of NSAIDs including CELEBREX has resulted in renal injury. Patients at greatest risk are those taking diuretics, ACE-inhibitors, angiotensin II antagonists, or with renal or liver dysfunction, heart failure, and the elderly [*see Warnings and Precautions (5.3, 5.6), Use in Specific Populations (8)*].

Patients should be instructed to promptly report to their physicians signs or symptoms of unexplained weight gain or edema following treatment with CELEBREX [*see Warnings and Precautions (5.3)*].

17.7 Anaphylactoid Reactions

Patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms [*see Warnings and Precautions (5.7)*].

17.8 Effects During Pregnancy

Patients should be informed that in late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus [*see Warnings and Precautions (5.9), Use in Specific Populations (8.1)*].

17.9 Preexisting Asthma

Patients should be instructed to tell their physicians if they have a history of asthma or aspirin-sensitive asthma because the use of NSAIDs in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Patients with this form of aspirin sensitivity should be instructed not to take Celebrex. Patients with preexisting asthma should be instructed to seek immediate medical attention if their asthma worsens after taking Celebrex [*see Warnings and Precautions (5.13)*].

17.10 GI Cancer in Familial Adenomatous Polyposis

Patients with FAP should be informed that CELEBREX has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX [*see Warnings and Precautions (5.15)*].

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Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.
This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?
NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?
Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	Other side effects include:
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- skin rash or blisters with fever
- unusual weight gain
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.

- Some of these NSAID medicines are sold in lower doses without a prescription (over –the –counter). Talk to your healthcare provider before using over –the –counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

* Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

EXHIBIT 179

2 of 24 DOCUMENTS

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SHOW: Talk of the Nation/Science Friday 2:00 PM EST NPR

December 16, 2005 Friday

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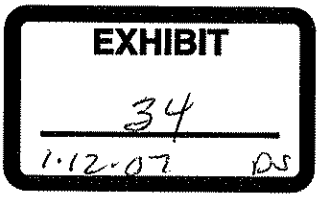

HEADLINE: Peer review

ANCHORS: JOE PALCA

BODY:

JOE PALCA, host:

This is TALK OF THE NATION/SCIENCE FRIDAY from NPR News. And I'm Joe Palca, sitting in for Ira Flatow.

You know, the term `breakthrough' gets tossed around pretty casually in the popular media, but in May of this year South Korean scientists published a paper in the journal Science that really lived up to the term. Hwang Woo-suk and his colleagues reported that they had used cloning techniques to create 11 embryonic stem cell lines tailored to match individual human donors. Scientists around the world hailed the remarkable achievement. This wasn't Hwang's first cloning triumph. He had created cloned cows and was the first to create embryonic stem cells from a cloned human embryo. So while his announcement in May was remarkable, there was no reason to doubt its veracity. Well, that was then.

Last month Hwang came under criticism for failing to disclose that eggs used in the research were donated by two junior women in his lab. That type of donation is frowned upon since there is the possibility that women might feel coerced into donating. And this week one of Hwang's co-authors, University of Pittsburgh researcher Gerald Schatten, asked that his name be taken off the paper, citing concerns about the data. Following that, another of Hwang's collaborators said Hwang had admitted to him that he had fabricated some of the data. Today, Hwang asked that the paper be retracted due to errors. He says he stands by the work and plans to repeat it. Science magazine is planning to have a teleconference on Hwang's request later this afternoon, and we'll bring that to you and tell you what the journal editors say later in this broadcast.

So far, charges that he fabricated results have not been proved. Lots of questions remain about what actually happened and who's telling the truth. Could a study using fabricated data make its way into a prestigious scientific journal? That's what we'll be talking about first this hour. If you want to get in on the conversation, I invite you to give us a call. Our number is (800) 989-8255; that's 1 (800) 989-TALK. And if you want more information about what we'll be talking about this hour, go to our Web site at www.sciencefriday.com, where you'll find links to our topic.

And now let me introduce my first guest this hour. First, **Catherine DeAngelis** is the editor in chief of the Journal of the American Medical Association. She joins us by phone from Chicago.

Thanks for talking with us today, Dr. DeAngelis.

Dr. **CATHERINE DeANGELIS** (Editor in Chief, Journal of the American Medical Association): You're welcome, Joe. Thanks for asking me to join you.

PALCA: And my second guest is Philip Campbell, the editor in chief for the journal Nature. He joins us by phone from London.

Thanks for being with us, Dr. Campbell.

Dr. PHILIP CAMPBELL (Editor in Chief, Nature): It's a pleasure, Joe.

PALCA: So, Phil Campbell, you have to leave in a few minutes, so I'd like to start with you. First of all, I think it's important that people understand that Nature and Science duke it out tooth and nail for the best scientific papers and so, you know, I would imagine that you would have been happy to receive this paper, but would you have been able, or can a scientific journal figure out in a peer review process that there was something so terribly wrong?

Dr. CAMPBELL: In principle, the answer is yes, but it's only on a minority of occasions that that seems to have happened in the history of fraud. There have been--there is quite an extensive history of fraud in the biological literature. There was a very notable case of fraud in the physics literature not so long ago, and in many of those cases a careful study shows that the peer refereeing process could not possibly have picked up what was fabricated because the peer reviewers do not go away and replicate the work before the paper is published, and, in many cases, it is only then, if then, that you'd be able to tell that something was drastically awry.

But then there are occasions, and we've certainly had our occasions, when we have been, perhaps, anonymously tipped off, or when a referee has actually spotted during the peer review process something suspicious about the data and that has led us to in the end reject a paper. And that has certainly happened to us.

PALCA: Well...

Dr. CAMPBELL: There are very few occasions, I have to say, when after publication in Nature a fraud has become clear to us and we've had to withdraw the paper.

PALCA: Well, maybe you can explain what a peer review--what a peer reviewer does. First of all, I guess, people should understand that a peer reviewer is somebody familiar with the field of literature that the paper is coming from and knows the science, but what does that person actually do when the paper is sent in?

Dr. CAMPBELL: It's a unique aspect of science as a discipline, as far as I'm aware, that people in science are willing to spend their time checking the work of colleagues to make sure that it's OK before it gets out into the light of day, as it were. But that is indeed what they do. Yes, they tend to be experts in one or another aspect of a piece of research. It could be a technical expert in terms of the technology being used; it could be a conceptual expert, if you like, looking at whether this represents a conceptual advance compared to what's been published before. Editors of journals have to supervise that process. They have to select the referees and they have to judge the comments made, and it's ultimately the editors that have to decide whether to publish the paper or not, so they do take responsibility but it is up to the referees, more often than not, anyway, to just be as sure as they can be, just based on what they see in front of them, in the written paper, whether or not this work looks credible, and I think that's the important point to make. All they can really do is to tell `Is this work credible based on everything I know?' What they're not doing, as I say, is going away and actually validating the work.

PALCA: But I'm just curious because if you look at some of the data, now that it's all post hoc, I grant you, but people have called attention to some of the figures in this paper by Dr. Hwang where two things that are said to be completely different, if you superimpose them, one on top of the other, you can see that they're identical. And, I mean, how does something like that slip past? Is it just because scientists say, `Well, I mean, I'm never going to question the data. The data must be accurate so I'm just trying to see if the results are accurate'?

Dr. CAMPBELL: Yes, well, of course, what I can't say is exactly what happened here because I don't think Science has actually made any statement yet and apparently they may do later on today as to exactly what is the nature of the data that they published in the terms that you've just said. It's certainly true that there seems to be--the data do seem to be suspicious just on sight. But as you also said, that is with the benefit of hindsight. It may be that exactly the right specialty was not available to the editors at the time that they assessed this paper. I mean, I'm not trying to let anyone off the hook here.

I mean, if I were in the editor's shoes here, I would certainly be going back through the process with a fine-tooth comb and just seeing exactly who was asked to assess the papers and whether or not they should indeed have spotted that and whether the editors themselves bear some of the responsibility here. It is possible that they do. But I have to say this is with the benefit of hindsight and I know from my own experience of cases where allegations have been made, or, indeed, we've published by mistake a paper that we shouldn't have because it wasn't peer-reviewed carefully enough. These things can slip through the net. And the only thing you can then do is quickly acknowledge the mistake and correct the literature.

PALCA: All right. So, Dr. DeAngelis, you're the editor of a medical journal which doesn't tend to publish quite as many basic science papers, but are the problems that you face with your referees and the papers that you get similar, or do you have a different set of problems?

Dr. DeANGELIS: Well, many of our problems are similar to my colleagues' in the basic sciences. We are the clinical sciences. The differences, I believe, are only in the scope of what we cover. Essentially, the papers we receive, especially those that are most open to fraud, if you will, are those that--from the clinical trials, for example. Those are very expensive to conduct. They involve numerous human beings. And therefore the statistics involved are sometimes the mechanism for fraud--for either deliberate or innocent reporting of something that isn't true.

So with us, the process is essentially the same as with my basic science colleague editors except that we--I don't know any large clinical science journal that would publish data-based articles without a basic science reviewer. And that isn't always necessary in the basic sciences because they are more descriptive, they often do not involve human beings and the numbers involved are small enough so that they're describing a process. That--those are the only differences. But we certainly, in the clinical sciences, the editors in the clinical sciences, have certainly found ourselves in positions where we discover by various mechanisms that what we've published is not the truth.

I mean, we have many examples. The **Celebrex** issue, which involved my own journal, where the report on a COX-2 inhibitor, the celecoxib, **Celebrex**--the report came out after six months. We knew, because of the protocol that we asked for, that the study was to go on for 12 months. We asked the authors did they have the 12-month data because the six-month data looked really interesting and something that physicians should know about because it showed that this drug worked and caused much less bleeding in the GI tract than...

PALCA: And so did the authors of--in this case, did they try not to tell you--did they say, `Well, we don't have the six...'

Dr. DeANGELIS: Well...

PALCA: ...`We don't have the 12-month data'?

Dr. DeANGELIS: They deliberately--they didn't try anything. They deliberately lied. We asked them...

PALCA: Ah.

Dr. DeANGELIS: ...three times and they said, `No,' and we published the paper as a preliminary. We stated...

PALCA: Right.

Dr. DeANGELIS: ...that it was a 12-month study, but we reported it as a preliminary study, but it was one that was--we put out very fast because if it were true it was...

PALCA: It would have been quite remarkable. I take your point.

Dr. DeANGELIS: It--yes, but the problem was...

PALCA: I take your point. Dr. Campbell...

Dr. DeANGELIS: I'm sorry. When they went out to 12 months, it turned out there was no difference. And then we got into trouble and we made them write a letter describing what they had done and admitting that they had lied to us.

PALCA: OK. Dr. Campbell, quickly, before you have to leave, one of the papers on the--one of the authors on the Hwang paper actually said he had very little to do with the paper. He was just the person who helped to present the manuscript. In about 15 seconds, can you tell me, is that a proper procedure? Can authors just have that little input?

Dr. CAMPBELL: I think that can be a matter of agreement between the authors, though--and I haven't actually read the statement that he made. It does sound a little bit too little, to me, to feel comfortable with. But it is certainly true that the role of co-authors and the responsibilities of co-authors is repeatedly shown to be a danger zone in this sort of area, and in the physics example that I mentioned where a whole string of papers turned out to be totally fraudulent, the work had been left--the central work had been left very much in the hands of one man. And that person is someone who's had to leave the field since. And the co-authors have...

PALCA: OK. Well, Phil Campbell, we have to stop you there. I'm really sorry. Have a good trip and thanks for joining us today.

This is TALK OF THE NATION from NPR News.

LOAD-DATE: December 17, 2005

EXHIBIT 180

Unknown

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Sent: Sunday, March 26, 2000 1:12 PM
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Cc: GEIS, GEORGE S. [PHR/1825]
Subject: FW: Special SMB Meeting

As per the note below, Phil wants us to present CLASS on Wednesday. Everyone has done a great job in putting together the interpretation, slide set and backup information. My suggestion is that we rehearse over the next couple of days so that we are all on the same page as we go into the meeting. Some of us will be in St. Louis over in the next day but we can go over things by phone.

Jim - do you want to distribute the main presentation to the addressees of this note?
Steve

-----Original Message-----
From: ISAKSON, PETER C [PHR/1005]
Sent: Saturday, March 25, 2000 12:52 PM
To: GEIS, GEORGE S. [PHR/1825]
Subject: FW: Special SMB Meeting

Sorry I will miss it, but I'm on vacation then.
PI

-----Original Message-----
From: MARKS, RICHARD A. [PHR/1825]
Sent: Friday, March 24, 2000 9:22 AM
To: GUALTIERI, ANN K. [FND/1820]; YOUNG, SALLY B [FND/1820]; PAPA, JOSEPH C [PHR/1820]; RASMUSSEN, NANCY D. [PHR/1820]; EDICK, PAUL R. [PHR/1820]; FORD, MIKE M [PHR/5430]; HAMELIN, PAUL R [PHR/1820]; JORDAN, DAVID C. [PHR/1825]; HAMELIN, PAUL R. [PHR/1820]; COUGHLIN, OLIVIA; GEIS, GEORGE; ISAKSON, PETER; MONTWILL, RICH; SCHAAF, JILL; FRIEDMAN, MICHAEL; HANSEN, LARRY; HELLER, ALAN; ISAKSON, PETER; JOHNSON, WILLIAM; MC KEARN, JOHN; MILLER, ARNI; MORRISON, CYNTHIA; NEEDLEMAN, PHILIP; SPIVEY, RICHARD; WARSCHAUSKY, CARL
Subject: Special SMB Meeting

NOTE: This meeting is only open to the people listed on this e-mail and the people Steve Geis invites from the clinical group.

There will be a special SMB meeting on Wednesday, March 29, from 9:30 - 12:00.

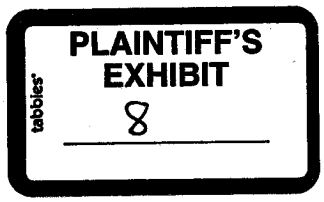
The purpose of the meeting is to have the CLASS data presented

The meeting will be in the Tundra Conference Room, A-Basement, Parkway

We have set up a teleconference access.

Teleconference number: 888-422-7109
Code: 942970

Rick Marks



Confidential - Subject To Protective Order

EXHIBIT 181

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
CIVIL NO. 03-1519 (AET)
(Consolidated)
CLASS ACTION

ALASKA ELECTRICAL PENSION FUND, CITY OF SARASOTA FIREFIGHTERS' PENSION FUND, INTERNATIONAL UNION OF OPERATING ENGINEERS LOCAL 132 PENSION PLAN, NEW ENGLAND HEALTH CARE EMPLOYEES PENSION FUND, CHEMICAL VALLEY PENSION FUND OF WEST VIRGINIA, and PACE INDUSTRY UNION-MANAGEMENT PENSION FUND, On Behalf of Themselves and All Others Similarly Situated,
Plaintiffs,

VS.

PHARMACIA CORPORATION, FRED HASSAN, G. STEVEN GEIS, CARRIE COX, and PFIZER, INC.,
Defendants.

****

ORAL & VIDEOTAPED DEPOSITION OF
DAVID Y. GRAHAM, M.D.
DECEMBER 21, 2011

****

ORAL & VIDEOTAPED DEPOSITION OF DAVID Y. GRAHAM, M.D., produced as a witness at the instance of DEFENDANTS, and duly sworn, was taken in the above-styled and numbered cause on the 21st day of December, 2011, from 9:15 a.m. to 4:48 p.m., before LORI A. BELVIN, CSR, and Notary Public in and for the State of Texas, reported by videographic and stenographic means, at the Law Offices of DLA Piper, L.L.P., 1000 Louisiana Street, Suite 2800, Houston, Texas, 77002, pursuant to the provisions of the Federal Rules of Civil Procedure.

APPEARANCES:

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ALSO PRESENT:
Mr. Dan Lapeyrouse, Videographer
Ms. Lori A. Belvin, Texas CSR No. 2572

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PROCEEDINGS

(The time is 9:15 a.m.)

THE VIDEOGRAPHER: We're now on the record. My name is Dan Lapeyrouse, CLVS, of Veritext. Today's date is December 21st, 2011. The time is, approximately, 9:15. This deposition is being held in the offices of DLA Piper, L.L.P., located at 1000 Louisiana Street, Suite 2800, Houston, Texas, 77002.

The caption of this case is Alaska Electrical Pension Fund, et al vs. Pharmacia Corporation, et al in the U.S. District Court, District of New Jersey, No. 03-1519. The name of the witness is Dr. Graham.

At this time, the attorneys will identify themselves and the parties they represent, after which, our court reporter, Lori Belvin, of Veritext will swear in the witness and we can proceed.

MR. SAHAM: Scott Saham for the Plaintiffs.

MR. DOUGHERTY: John Dougherty with Mike Wigotsky at DLA Piper for the Defendants.

(Witness sworn under oath by the reporter.)

THE REPORTER: On the record.

* * *

DAVID Y. GRAHAM, M.D., M.D.,
having been first duly sworn, testified as follows:

* * *

EXAMINATION

BY MR. DOUGHERTY:

Q. Good morning, Dr. Graham. Sorry it took -- it's difficult to find this place. So I apologize for that.

You've been deposed before, I take it?

A. Yes.

Q. Okay. How many times do you think?

A. Five or six.

Q. Okay. So, you know the ground rules. I'm going to get a chance to ask you questions. You get a chance to answer. All of your answers have to be verbalized so that the court reporter can take them down.

Let me ask you about your work as an expert witness. You've been designated as an expert witness in this case; is that correct?

A. Yes.

Q. And have you been designated as an expert witness in any other case --

A. Yes.

Q. -- in your career? And can you just describe those assignments for me?

A. Well, I've been an expert witness in a Rofecoxib

trial against the State of Louisiana, against Rofecoxib against Merck.
Q. Right.
A. And, then, I've been expert witness in several patent cases in Canada, where the drug companies were seeking patents or extensions and the other companies were arguing against that.
Q. Okay. Any other expert witness assignments that you recall, sir?
A. Well, years ago, I did some -- one pharmaceutical company suing another over advertisements.
Q. Okay. All right. Has that been more than ten years ago, do you think?
A. More than ten years ago.
Q. Okay. In the Vioxx case, that was a case where the State of Louisiana was suing Merck and there was a trial in that case, was there not?
A. There was a trial.
Q. And that trial was in Louisiana?
A. In New Orleans, right.
Q. In New Orleans?
A. (Witness nods head.)
Q. And you appeared as an expert witness in that case for the plaintiff, did you not?
A. Right.

Q. Okay. And can you describe for us, just generally, what the opinions were that you offered in that case or what you understood your assignment to be?
A. My assignment was related to the -- the question about whether the drug was effective as had been reported in a paper, published in the New England Journal.
Q. Was that the VIGOR trial?
A. The VIGOR -- the Vioxx trial, yeah --
Q. But which --
A. -- the VIGOR study.
Q. The VIGOR study as published in the New England Journal of Medicine?
A. Right.
Q. And that involved Vioxx?
A. Yes.
Q. And did you offer the opinion in the Vioxx case, Dr. Graham, that Vioxx was no better than traditional NSAIDs when it comes to efficacy?
A. That's what I offered, yes.
Q. Do you believe that?
A. That was what the data say.
Q. No, but I'm asking you, sir: Do you believe it?
A. I didn't know that medicine and science worked in the "belief" business. We're evidenced-based and the

evidence did not support that.
Q. So, it's your opinion that Vioxx is no better than traditional NSAIDs when it comes to efficacy?
A. That's what the data showed.
Q. I understand that's what the data shows; but, Dr. Graham, I'm asking you if that's your opinion?
A. That's my opinion.
Q. And does that opinion hold true for all patients or only some patients?
A. I don't understand the question.
Q. Are there some patients that take Vioxx and have better results from an efficacy standpoint than other patients?
A. Oh, any drug, yeah, there's some variation among patients' perception or their actual benefit. Even placebo has a 40 percent response rate in many trials.
Q. But you -- are you -- do you treat patients, sir?
A. Yes.
Q. If somebody came into you complaining about the signs and symptoms of arthritis, would you give them placebo or Vioxx, if those are your only two choices?
A. That would be hard a decision now, considering I'd have to worry about their cardiovascular risks and other problems. It may well be that placebo might be a better choice.

Q. Do you prescribe placebo to your patients, Doctor, ever?
A. Probably all the time not knowingly.
Q. Not knowingly.
A. It may well be.
Q. And do you have a script for placebo that you write?
A. No, no.
Q. And did you offer any opinions in that Merck trial, Doctor, about the gastrointestinal safety of Vioxx relative to traditional NSAIDs?
A. That's what the trial was about, basically -- at least my part of the trial was about.
Q. So, the answer to my question would be, "yes," you did offer those opinions?
A. Yes, yes.
Q. Okay. And. Can you summarize for us what those opinions are?
A. Well, they had done a large trial to ask whether or not it was safer as far as major GI events; and they had reported that they had found a difference and that question -- that hypothesis or conclusion was called into question when the data were analyzed in a more appropriate way.
Q. Analyzed by who?

A. Well, by the statisticians and by many people. I mean, I think it's pretty well accepted now that that was an incorrect interpretation of data.
Q. Did you offer an opinion in the Vioxx trial, Dr. Graham, that Vioxx, based upon the results of the VIGOR trial, did not show a GI advantage over Naproxen?
A. I -- for safety?
Q. Correct.
A. All of the benefit that they had showed was in one group, which was those taking -- concomitantly taking corticosteroids. And the other group, people not taking corticosteroids, there was no evidence of benefit.
Q. And did you conduct an analysis to support that opinion in connection with your assignment in the Vioxx case?
A. I don't do those kind of analyses, no.
Q. Okay. But you did publish the results of such an analyses, didn't you?
A. Right.
Q. So, describe to me when you did, if that was not part of your assignment in the Vioxx trial?
A. Well, there were three authors in the paper, including the statistician who actually did the analysis.

Q. So, what was your contribution to that paper?
A. The analysis of the -- was one part of that paper. That paper discussed the whole approach to how one answers the question and not only was restricted to that one question, but to other events, for example, lower gastrointestinal bleeding, which was another claim that the paper that had been written said that it was safer for lower gastrointestinal bleeding and that was made on an inappropriate way.
Q. Inappropriate according to you?
A. I think inappropriate according to anyone. I mean, the person who chose to subgroup, which it was statistically significant only did so after the code was broken and it was not the original subgroup that was chosen, if you like, blindly. So it was a -- it was just not the way science is done.
Q. Is it your opinion, Dr. Graham, that the results that you present in the paper that you're a co-author on, on Vioxx, is more scientifically reliable than the New England Journal of Medicine's presentation of those data?
A. I think the New England Journal paper actually should be withdrawn and -- because it was flawed, greatly flawed. The reviewers of the paper had had asked similar questions that we addressed and did not

get honest answers for Merck.
MR. DOUGHERTY: Madam Reporter, can you read back my question for the witness, please?
(Question read back for the record.)
MR. SAHAM: Objection, asked and answered.
Q. (BY MR. DOUGHERTY) Can you answer my question, Dr. Graham?
A. The conclusions of the New England Journal paper we showed were in error. And if you say that's the definition of "scientifically accurate" would be they were in error and we showed that that was in error, then they were inaccurate.
Q. Do you believe that your analysis of the VIGOR data as presented in the paper that you co-authored is more scientifically reliable than the New England Journal of Medicine article?
MR. SAHAM: Objection, asked and answered.
And if he's asking the question again, you can answer it again, Doctor.
A. Yes.
Q. (BY MR. DOUGHERTY) Okay. Thank you, sir.
The patent cases that you were an expert in, do you recall who you were testifying or who you were retained by in those cases?
A. Different generic companies.

Q. And in each case, was that generic company challenging the patent of another pharmaceutical company?
A. Yes.
Q. And you were working on behalf of the company that was trying to either get around or invalidate those patents?
A. I was giving opinions about the validity of the patents, yes.
Q. Okay. And can you tell me what the results were in each of those cases where you testified for the generic?
A. I don't remember exactly how many there were, but the generic company prevailed or won in all but one.
Q. Okay. Can you tell us what the medicines or drugs were in those cases?
A. They were proton pump inhibitors, like omeprazole.
Q. In each case each, you're -- each patent case you've been in you were testifying on behalf of a generic company challenging patents covering PPIs?
A. In all their cases into Canada, yes.
Q. And in the Vioxx case, just to move back to that really quickly, do you recall what the result was in the Vioxx trial, whether the plaintiffs prevailed in that

case?
A. My understanding is that the judge said that the State of Louisiana had no choice, if their data were right or wrong, if the FDA had approved the drug, they had to pay for it, no matter what.
Q. So that means the plaintiffs lost in that case; is that your understanding?
A. That's my understanding.
Q. Are there any other expert witness assignments, other than the ones we've just discussed, that you've been involved in, obviously?
A. Not in the last ten years.
Q. Have you ever acted as an expert witness on behalf of a pharmaceutical company that's not a generic pharmaceutical company?
A. Ye.
Q. And can you describe those assignments?
A. Well, I did another patent, if you like, about a drug called Slow-K and one called Micro-K, potassium preparations. There was one called Micro-K. It was the Robbins company at the time had it.
Q. And you testified on behalf or you acted as an expert on behalf of the non-generic pharmaceutical company in that case?
A. They were both non-generic companies, yes.

Q. Okay. And those are the Robins cases, is that --
A. The Robins, it was non- -- it was a regular company; and the other one, I think, was CSUGIE, the one that I was testifying for.
Q. Okay. And how long ago were those assignments?
A. 15 or more years.
Q. Dr. Graham, have you done any original research on COX-2's?
A. I've done pharmaceutical companies and original research on COX-2's, yes.
Q. Okay. And can you describe that work?
A. Well, I did some of the clinical trials, where we gave people coded blinded drugs and, you know, turned in the data. And I did my own studies where I fed people different NSAIDs and looked at the effect on ulcer healing in the stomach.
Q. Anything else?
A. Not specifically, I think, for COX-2's.
Q. Okay. So with respect to COX-2's, the original research that you've done has either been clinical trials funded presumably by the sponsoring company and some studies that you've done on your own; is that -- do I have that correct?
A. Right.

Q. Okay. And the clinical trials that you've been involved in that were sponsored by the company, can you identify those for us, please?
A. Not specifically. I mean, I can't give you the name or number of the trial. There were many of those trials that were done early on when they were first doing these drugs, and we did drug trials both with Celecoxib and with Rofecoxib.
Q. Now, you used the term "we." Is that referring to you and others, or is that the "Royal We" when you're referring only to yourself?
A. Well, there's more than one of us that does clinical trials, I mean, in a group at Baylor. I mean, I would be the PI.
Q. Okay. You'd be the principal investigator on these trials?
A. Right.
Q. And you said that you were involved in conducting clinical trials involving both Celebrex and Vioxx; is that correct?
A. I think so, yes.
Q. And tell us what you can remember about your involvement in any clinical trials involving Celebrex.
A. Well, that I was involved in some of the very early trials when we were testing it against other

NSAIDs and placebos for endoscopic ulcers. I'm actually involved in a current trial with Celebrex.
Q. The Precision trial, sir?
A. The Precision trial.
Q. And the primary endpoint in that trial is -- it has to do with a cardiovascular risk; is that right?
A. Cardiovascular.
Q. Okay.
A. It's looking at all aspects, but it focuses on cardiovascular.
Q. And what is the primary endpoint of Precision, Dr. Graham?
A. I mean, the main question is "Do the drugs differ in their cardiovascular safety?"
Q. And what is the primarily endpoint in Precision?
A. It's events like heart attacks, strokes.
Q. Just thrombotic events or other events, other cardiovascular events?
A. The focus is on, I mean, heart attacks; but it's any cardiovascular event.
Q. Well, the primary endpoint isn't any cardiovascular event, is it?
A. If you want the exact primary endpoint, I cannot give it to you.
Q. Okay. That's fair. And if you don't know, you

can say you don't know.
A. I have no problem with "I don't know."
Q. Okay. So let's talk about the Vioxx trials for a second. What clinical trials have you been involved in relating to Vioxx?
A. I don't remember any details. I just remember that we did some studies where we've had, you know, two coded drugs to people and did endoscopic procedures.
Q. Was that similar to what you did for Celebrex?
A. Similar model.
Q. Okay. Do you recall how many clinical trials you were involved in for either Celebrex or Vioxx?
A. No.
Q. Were you involved in the CLASS trial?
A. I don't think so -- "no."
Q. What about the VIGOR trial?
A. No.
Q. So, is it fair to say that your recollection of the clinical trials that you've been involved in using either Celebrex or Vioxx have been endoscopy studies?
A. Mostly endoscopy studies.
Q. And, in fact, one of those trials, Dr. Graham, resulted in a publication in JAMA where you're listed as a co-author; isn't that right?
A. Yes.

Q. What role, if any, did you have, Dr. Graham, in designing those endoscopy trials for Celebrex?
A. The actual trial?
Q. Correct.
A. Very little. I mean, the trial design is -- by that time was pretty standardized, a cookie-cutter type of approach to these questions.
Q. Did you review the protocol before agreeing --
A. Oh, absolutely.
Q. -- to become an investigator on any of those trials?
A. Oh, absolutely.
Q. Did you have any problem with the protocol?
A. Not that I remember.
Q. Did you remember having any problem with the design of those clinical trials?
A. They were standard clinical trials for those questions.
Q. I appreciate that, but my question was: Do you recall having any problems with the design?
A. I don't recall.
Q. Okay. Do you recall what the results of the endoscopy trials for Celebrex was?
A. It was shown that for endoscopic ulcers that Celebrex was less likely to cause endoscopic ulcers and

less likely to cause symptoms than traditional NSAIDs. That was, at least, the comparatives and the doses used.
Q. Is that what the data showed?
A. That's what the data showed.
Q. Did you have any reason to question the validity of those data?
A. No.
Q. And, today, do you have any reason to question the validity of those data?
A. No.
Q. And, so, you stand behind the paper that you co-authored in JAMA regarding the results of Celecoxib in the endoscopy trial that you were involved in?
A. Yes.
Q. And do you recall working with any employees or scientists, sir, from G.D. Searle on those trials?
A. I mean, I interacted with the people at Searle because I was involved before that with Misoprostol, which was the predecessor drug, if you like, same people.
Q. In your work on Misoprostol, Dr. Graham, can you describe for us what that involved?
A. Same. I only did endoscopic trials and they were -- it addressed whether it was useful as a safe drug.

Q. And what were the results of those endoscopy trials --
A. I mean it showed --
Q. -- involving Misoprostol?
A. -- it showed Misoprostol was effective in reducing or preventing ulceration from NSAID-induced ulcers. It was good hypothesis that was proven.
Q. And do you still believe those data are valid?
A. Absolutely.
Q. And do you recall whether there was more than one trial involving Misoprostol that you were involved in?
A. Yes.
Q. More than one endoscopy trial?
A. Right.
Q. Do you recall whether the primary endpoints in those trials were the same or different?
A. Not specifically. Presumably they were all very similar because that was -- it's a model.
Q. In your opinion, Dr. Graham, were those trials clinically useful at all?
A. I don't understand the question.
Q. Sure. The data that came out of those trials involving Misoprostol, were they of any clinical use?
A. Oh, unquestionably. We --
Q. How so?

A. Well, that was the MUCOSA trial that was done, which was the first trial to show that you could prevent or reduce the frequency of these serious adverse effects.
Q. And could you describe how that information was clinically useful?
A. Well, the main problem with the use of NSAIDs is that people have major GI events, bleeding, perforation, obstruction; and the trial was done to ask whether the co-therapy with Misoprostol would reduce those untoward effects, and it showed that it did.
Q. Turning now to the endoscopy trials that you did on Celebrex, was there any clinically useful information coming out of those endoscopy trials?
A. The hypothesis for Celebrex was that the COX-2 inhibitors would -- selective COX-2 inhibitors would not cause GI damage or would markedly have reduce rates of GI damage. And, so, the original trials were designed to see if that hypothesis was supported by the data.
So, yes, they were very useful because they showed that it tended to support that hypothesis, which led to the next -- designed next studies.
Q. So just to make sure that we have a common foundation here, Dr. Graham, isn't it fair to say that the endoscopy trials involving Celebrex showed a GI

advantage for Celebrex over the NSAIDs that were tested in those trials?
MR. SAHAM: Objection, misstates prior testimony.
A. Within the parameters of the trials and their weaknesses, et cetera, and their doses, et cetera, they tended to show -- they routinely showed that there was a difference.
Q. (BY MR. DOUGHERTY) Are you aware of any endoscopy data comparing Celebrex to a traditional NSAID that doesn't always favor Celebrex over the traditional NSAID?
A. Companies never tend to want to do a study that predictably is going to come out and not show what they want to show. So I don't know if such studies were done. I know such studies were done with Vioxx and that they were not published, at least, initially. I don't know if similar studies were done with Celebrex and not shared. I wouldn't be surprised.
Q. So, the short answer to my question is you're not aware of any studies comparing Celebrex to an NSAID and any endoscopy studies comparing Celebrex to an NSAID that don't favor Celebrex in the results of those trials?
MR. SAHAM: Objection, form, asked and

answered, misstates prior testimony.
A. I know personally of no such trials.
Q. (BY MR. DOUGHERTY) Any do you believe that those endoscopy data coming from the endoscopy trials involving Celebrex, do you believe those data are clinically useful?
A. Clinically useful? I don't know -- I don't really understand the question. They're clinically useful, only in that they support the hypothesis and leads you to continue the research.
Q. Do you believe that those endoscopy trials proved any GI advantage for Celebrex over traditional NSAIDs?
A. No.
Q. And, yet, you're a co-author on a JAMA article presenting the results of one of those trials; isn't that correct?
A. Oh, yes.
Q. And you understood that when you published that article that practicing physicians would read it?
A. Yes.
Q. And you understood that -- and you attempted to communicate in that article information that would be clinically relevant to those physicians, did you not?
A. Well, they're clinically relevant as far as the hypothesis we were testing was concerned, yes.

Q. I don't understand what you mean "the hypothesis we were testing."
A. The hypothesis was that the COX-2 hypothesis was correct, that hypothesis COX-2's didn't -- wouldn't cause the same side effects that the NSAIDs -- traditional NSAIDs caused.
Q. That was the hypothesis going into those trials, correct?
A. Going into the trials.
Q. And that relates back to the work that was done in the late '80's and early '90's that developed the so-called the COX-2's hypothesis, correct?
A. Right.
Q. And the clinical trials in Celebrex that you were involved with confirmed that hypothesis based upon the endoscopy data?
A. Based upon the endoscopic model.
Q. And you believe those data are valid still today?
A. They were good studies.
Q. And you believe those data are still valid today, correct?
A. They're still valid today within the context that they were done, yes.
Q. And it's still important for physicians to understand the results of those trials, don't you agree?

A. Well, I'm not sure of that. I mean, the world's moved on beyond there to test the other hypotheses.
Q. Fair enough.
For the time you published the JAMA article in one of those trials, you thought it was important for physicians to understand that the data confirmed the hypothesis, correct?
A. Oh, sure.
Q. Can we talk about the clinical studies you, yourself, have done involving COX-2's? Is it okay if we shift to that now?
A. (Witness nods head.)
Q. Okay.
A. Whatever you want.
Q. What COX-2's have you tested yourself?
A. Celebrex.
Q. Okay. And did you publish the results of any of those tests?
A. Well, we have -- we published in an abstract format. The paper's been written, but not been submitted yet.
Q. Could you just explain that a little bit further?
A. Well, you do the study and you analyze the data and then you, typically, present it somewhere as an abstract paper, you know, a poster or something at a

national meeting. And, then, you finish it up and you submit it to a journal and it's published.
Q. And has the abstract for that -- first of all, how many trials have you done yourself involving Celebrex?
A. That weren't supported by Celebrex?
Q. That weren't supported by the company that marketed the medicine.
A. Only one.
Q. And what is that trial?
A. And that was a trial asking about ulcer healing and experimental ulcer healing in humans.
Q. I'm sorry. "Experimental ulcer healing," I don't know what that means. Can you describe it for me, please?
A. Well, you take big biopsy forceps and you do a biopsy which causes an acute ulcer and then you give the patient drugs and you endoscope them every few days and you measure the rate of healing.
Q. How many -- was this conducted on humans?
A. Yes.
Q. And how many people were in that trial?
A. Maybe 50.
Q. Were these patients at Baylor?
A. Volunteers.

Q. Can you -- and you went in and caused them an ulcer so that you could study the ulcer healing process in them?
A. Yes.
Q. What was the inclusion/exclusion criteria for those patients?
A. Healthy.
Q. NSAID users?
A. No.
Q. What was the average age of those folks?
A. 30's.
Q. Not the traditional kind of people that take Celebrex, wouldn't you agree?
A. I mean, the question was a different question than -- and you wouldn't do that same question in a person who, if they had a problem, would have an untoward event. But, normally, when we take a gastric mucosa biopsy with large forceps, you actually cause an ulcer.
Q. In fact, that's what you wanted to do in that trial, is cause an ulcer and study the healing process?
A. That's right. We cause ulcers every day, but they're acute and heal right up.
Q. Other than Celebrex, were there any other therapies studied in that trial?

A. Yes, yes.
Q. And what were they?
A. We looked at Nabumetone.
Q. What is that?
A. That's another NSAID.
Q. Does anybody ever use it in the United States?
A. Relafen, it's very widely used. It's considered the safest of the NSAIDs.
Q. We'll come back to that, because you're going to need to support that statement.
A. And I think Naproxen, a placebo.
Q. Naproxen is "over the counter," is it not?
A. Yes.
Q. Is Relafen "over the counter"?
A. I think so now.
Q. Do you know what the trade name for it is?
A. Huh?
Q. Do you know what the trade or brand name is?
A. Relafen is the trade name. Nabumetone is what its real name is. It's an old SmithKline, I think, drug.
Q. And do you have a proto- -- is there a protocol for this trial somewhere?
A. Sure.
Q. And who else was involved in this trial?

A. I mean, the people that work with me. It was published in Gastroenterology last year.
Q. And what did the trial show?
A. It showed that --
Q. Let me put it that another way. Let me withdraw that question.
A. Yeah.
Q. What did the trial prove?
A. (No audible response.)
Q. You're smiling.
MR. SAHAM: Objection to form.
A. It -- I don't know if it proved anything. It showed that ulcer healing occurred irrespective of the NSAIDs that we were giving and they all seemed about the same as far as one another. And it was actually supported by the people who made Nabumetone, who didn't like the answers.
Q. (BY MR. DOUGHERTY) I was just going to ask who funded this study?
A. Nabumetone.
Q. And what's the company's name?
A. I think it was SmithKline at the time or it may have been somebody else. I don't know who did it. It was about ten years ago.
Q. The study was about ten years ago?

A. Yes.
Q. Okay. I thought you said it had been presented, but not published. Maybe I misunderstood you.
A. We finally presented it this year.
Q. Presented it to which journal?
A. Well, we presented it at the DDW. It's published in Gastroenterology, and we'll submit the paper right after the first of the year.
Q. And I just want to make sure I got it. You did a clinical trial ten years ago?
A. Right.
Q. And only this year did you present the results?
A. Right.
Q. Why did you wait so long?
A. The sponsor was very unenthusiastic about the data and negative about the data and we just let the world -- since no one else is doing that experiment, there's no rush and let the world take a few turns and then people retire and then we present the data.
Q. But you could have presented that data when you completed the trial, right, Dr. Graham?
A. Could have.
Q. But you didn't?
A. Didn't.
Q. How much did the trial cost to conduct?

A. I don't remember. It wasn't much. I mean, it was probably 20, $30,000; and we did it at cost.
Q. Was there any important information coming out of that trial, clinically important information?
A. No data that were -- I mean that was going to change practice.
Q. Okay. Is that the reason why you waited ten years to publish?
A. Yeah, it's just kind of an interesting fun study that will get published and like the rest of the papers, just kind of disappear somewhere.
Q. Dr. Graham, does H. Pylori cause peptic ulcers?
A. Yes.
Q. Is that your scientific opinion?
A. Well, it's considered dogma now. It may not be true, but that's the current dogma.
Q. Forget about dogma. I actually want to know what your opinion is, Doctor. Does H. Pylori cause peptic ulcers?
A. Yes.
Q. Have you always held that view?
A. Well, after the data became evident, yes.
Q. But before the data become evident, you actually took the opposite position, didn't you, rather publicly in questioning whether H. Pylori caused peptic ulcers?

MR. SAHAM: Objection to form.
A. I took the position that it was a hypothesis, it was testable, and that -- that's different than what you said.
Q. (BY MR. DOUGHERTY) Well, we can pull out your article --
A. Yeah.
Q. -- and look at it.
A. I'll be happy to do that.
Q. Okay. Wouldn't it be fair to say -- if I asked some of your colleagues who have known you for a long time, that you were very skeptical of whether or not H. Pylori caused peptic ulcers and you were very vocal on that question back in the '80's; isn't that fair?
MR. SAHAM: Objection to form, foundation.
A. I don't think so.
Q. (BY MR. DOUGHERTY) Have you ever conducted a clinical trial, Dr. Graham, or been involved in the conduct of a clinical trial that uses perforations, obstructions, and bleeding as a primary endpoint -- perforations, obstructions, and bleeding?
A. I was involved in the MUCOSA trial.
Q. Other than that?
A. No.
Q. Other than the VIGOR trial and the CLASS trial,

Dr. Graham, are you aware of any other large clinical trials conducted involving NSAIDs that use perforations, obstructions, and bleeding as an endpoint?
A. I presume that the other -- the other -- as a different endpoint? "Probably not." I mean, this is a requirement to get approval to eliminate the CLASS labeling. And I don't know if the other companies that make COX-2's went out to prove that CLASS labeling or not.
Q. Just to make sure I understand your answer, other than CLASS and VIGOR, the CLASS and VIGOR trials, you're unaware of any large scale clinical trial conducted that uses perforations and obstructions and bleeding as an endpoint; is that fair to say?
A. They may exist, but I don't know any specifically.
Q. Dr. Graham, how many clinical trials have you been involved in that use death as an endpoint for a gastrointestinal safety?
A. I would think all trials use death as an endpoint, but not as a prespecified, I mean, endpoint because all studies are interested in deaths that might occur. But they're not set out to measure death as an outcome.
Q. Perhaps you and I should just kind of have a

common vocabulary. What's an "endpoint"?
A. Start with "What is a clinical trial?"
Q. No, just tell me what an "endpoint" is.
A. An "endpoint" is a word that says it's an outcome.
Q. Okay. And what's an endpoint when we talk about that -- use that term in the context of clinical trials? What does that mean?
A. Any clinical trial you get to define 1) outcome, that is, your primary outcome that decides what the trial succeeds or fails.
Q. And in the vocabulary of scientists and doctors and clinical trialists, you agree that there's only one endpoint for each clinical trial? Is that what you're saying?
A. There's one major endpoint for each clinical trial, the one that use that's prespecified, yes. And I think that I have involved in trials that used death as an endpoint.
Q. Okay. Tell me which trials those were.
A. Those would be trials looking at treatments for bleeding, such as variceal bleeding, soft GI varices. And my unit has done a bunch of those with early banding and sclerotherapy where death was one outcome.
Q. Well, there can only be one outcome, right,

according to you. So using the definition, the "one outcome" definition, are you saying that you were involved in trials where the outcome being studied was death?
MR. SAHAM: Objection to form, misstates prior testimony.
A. That's a very complicated outcome, okay? For example, if you were doing a bleeding study for a variceal bleeder and you'd say that one of the outcomes would be -- was your therapy effective and, then, what proportion of your patient died within this time frame. It's like a cancer outcome. It has a very high mortality rate for the disease. And, so, if it's a dichotomy, survival versus death or re-bleed versus no re-bleed or rebleed with death, it becomes -- you know, the outcomes become very complicated.
Q. (BY MR. DOUGHERTY) "The outcomes," is that what you said?
A. The individual trial becomes very complicated.
Q. Okay. So, going back to my question: What trials are you aware of that are testing GI safety where the outcome -- because you said it could only be one outcome in each trial -- the outcome is death?
MR. SAHAM: Objection, form.
Q. (BY MR. DOUGHERTY) Just name them for me.

MR. SAHAM: Objection, form.
A. It would be studies having to do -- most of them would have to do with GI bleeding.
Q. (BY MR. DOUGHERTY) And what you don't do -- I'm sorry?
A. Treatment of bleeding ulcers or bleeding varices.
Q. Okay. Would those involve the study of the -- any of those involve the study of the effects of NSAIDs on that outcome?
A. I don't know of any studies of the effect of NSAIDs on those outcomes, no.
Q. Do you believe that it would be ethical, Dr. Graham, to conduct a clinical trial comparing the relative GI safety of NSAIDs where the outcome being studied is death?
A. I don't know if it would be ethical or not, but I cannot imagine the design. That would be the primary outcome.
Q. Would you sign up for such a study?
A. I would have to read the protocol, but I would be very hard-pressed to sign up for that study.
Q. Because the outcome is death?
A. Well, no, the outcome is irrelevant; but it's -- you could say -- it's hard to imagine what you would do that had that outcome that would be a clinically

valuable study that people would want to know.
Now, we're not that far away looking at cardiovascular risks, though, with NSAIDs now, that one of the outcomes of that will be death or myocardial infarction, which is considered by many equally death. So, you could say, therefore, possibly we're looking at that in an indirect way right now.
Q. I agree with you in an indirect way, but not in a direct way. Your event -- your events that you're studying in Precision are not death. You're looking for thrombotic events, correct?
A. Well, death is one you're going to measure. I mean, it's clear that when you gave people cardiotoxic drugs that you have more deaths because of the drug than you would have if you didn't give the drug and NSAIDs were responsible for those deaths. And that's what we're trying to reduce, is deaths basically because of the use of NSAIDs. So, in reality, we're doing those studies today.
Q. Even if that's not the endpoint of the study?
A. I'm sure it's one of the endpoints.
Q. I thought we agreed there could only be one endpoint?
MR. SAHAM: Objection, misstates prior testimony.

A. You can have multiple endpoints. You only get one at the outset that count whether the study won or failed.
Q. (BY MR. DOUGHERTY) Okay. But you can collect data on other events that get observed in the conduct of the trial, correct?
A. That's right.
Q. And those data may be clinically relevant and in some cases extremely relevant to clinicians, correct?
MR. SAHAM: Objection to form.
Q. (BY MR. DOUGHERTY) Go ahead.
A. They might be, yes.
Q. For example, death as an event, it's -- would be relevant, correct?
A. It's collected in every trial because it would be relevant.
Q. And it's reported in every trial, even if that's not the primary endpoint, correct?
A. Yes.
Q. And there are other information that you're collecting in a clinical trial that are going to be relevant to clinicians even if it's not the primary endpoint, correct?
A. Well, it may be relevant and it may not be. You know, you hate to throw away information. The question

is how do you use the information.
Q. All right. Fair enough.
In fact, you've published a lot, Dr. Graham, and isn't it fair to say that a lot of your publications are describing the results of clinical trials and focusing on results that are not, in fact, the primary endpoint of that study?
A. Well, I don't know if they focus on the things that are not the primary endpoint; but they certainly would describe some of them.
Q. And in some cases you describe them in great detail, do you not?
A. Well, you'd have to give me some examples, but I might.
Q. All right. Well, you have a long list and I'm sure there's plenty in there.
A. (Witness nods head.)
Q. And if you want to fight me on it, we can go and look at them; but I think you've given me the answer that's the honest answer, which is, "yes," you do talk about that?
MR. SAHAM: Objection, form, foundation, misstates prior testimony.
Q. (BY MR. DOUGHERTY) Do you believe the CLASS trials should have had death as the outcome, the primary

endpoint?
A. No.
Q. Dr. Graham, we're going to mark your report that you submitted in this case as an exhibit so that you have it in front of you -- and you may have it already next to you, but we've got to make this official.
MR. DOUGHERTY: Could you mark that as 1054? Scott (hands document to Mr. Saham).
MR. SAHAM: Thanks.
(Exhibit No. 1054 marked.)
MR. SAHAM: Oh, this is the rebuttal -- oh, well, I'm sorry.
MR. DOUGHERTY: He's only submitted one.
MR. SAHAM: Yeah, that's right.
Q. (BY MR. DOUGHERTY) Dr. Graham, you have in front of you what's been marked as 1054. It's entitled the "Rebuttal Report of David Y. Graham, M.D." That's you, right?
A. That's me.
Q. And did you write this report, sir?
A. Yes.
Q. And does this report contain the opinions that you intend to offer in this case?
A. I mean, that's my opinions, yes.
Q. All right. And, Dr. Graham, since writing this

report -- and I'll just note that you dated it July 7th of this year -- other than the opinions offered in this report, do you intend to offer any other expert opinions in this case?
A. I don't intend to. I mean, I might; but I don't intend to.
Q. Well, you realize that I would have the opportunity to kind of understand and question you about those opinions. So, sitting here today, other than the opinions expressed in this report, are there any other opinions that you intend to offer in this matter?
A. No.
Q. Dr. Graham, if you go to Page 20 of your report.
A. (Witness complies with request.)
Q. There is a -- I'm going read a sentence of your report into the record -- and it really starts, actually, on the bottom of Page 19. Do you see that sentence that says "This was an exercise in futility"?
A. Yes.
Q. Okay. So I'm going to continue reading there, quote "...as clinical trials can have only one endpoint." And that's what we were just talking about earlier, right, that clinical trials can have only one endpoint; is that right?
A. One endpoint for, yes, for validity -- for the

trial, "win" or "lose."
Q. Right, and that's -- we get to the next sentence in your report; and I'll read it to you. Quote, "If one fails to disprove the null hypothesis," the studies fail -- the study fails and any other analyses and, as noted above, any conclusions become hypothesis generating subgroups that can either be prespecified or that appear interesting following data inspection."
Did I read that correctly?
A. Yes.
Q. That's your opinion?
A. Yes, that's my opinion.
Q. You stand by that opinion?
A. Yes.
Q. In all of the research that you've co-authored or co-author on, do you ever discuss in any of those publications what you're calling "hypothesis generating subgroups"?
A. Yes.
Q. And would you agree with me, Dr. Graham, that the reason that you're publishing these so-called "hypothesis generating subgroups" is that you think that information is potentially relevant?
A. Yes.
Q. And in some instances, over the course of time,

those hypothesis, what you call the hypothesis generating subgroups can either be confirmed or disproven, correct?
A. Well, that's -- they are hypotheses. They're to be tested.
Q. Was the COX-2 hypothesis tested before CLASS?
A. Was the hypothesis tested before CLASS? CLASS was the test of the hypothesis, right.
Q. No, I'm asking you a different question, Dr. Graham. I'm asking you whether the hypothesis, the COX-2 hypothesis, had been tested before CLASS?
A. I'll answer you the same way: The hypothesis was that the COX-2 inhibitors would not damage the mucosa and that the major complications that we see with NSAIDs, bleeding, perforation, obstruction would, therefore, effectively, the hypothe- -- they would not occur, which in scientific basis which would be that they would be statistically less prevalent than even with placebo.
Q. Are you saying that the COX-2 hypothesis is that GI adverse events would never occur in a COX-2 inhibitor population?
A. Well, under the hypothesis, you would think they would never occur; but, then, you say, "Well, there are other causes so, therefore, there's some background."

Q. Fair enough.
And, in fact, Dr. Graham, you were involved in testing that hypothesis before CLASS, correct?
A. We were doing -- collecting data to not necessarily test the hypothesis. In fact, I think the paper, in the JAMA paper, makes it very clear that we were not comparing against placebo. We were collecting data to support that building up to this study, which actually tested it.
Q. Are you familiar with the FDA's approval of Celebrex?
A. No.
MR. SAHAM: Objection, form.
Q. (BY MR. DOUGHERTY) That's a broad question. Let me -- are you aware of whether or not the FDA had accepted as proven the COX-2 hypothesis prior to approving Celebrex for marketing in the United States?
MR. SAHAM: Objections, form, foundation.
A. I am not aware of that.
Q. (BY MR. DOUGHERTY) Are you familiar with all the studies that were supported in -- or submitted in support of the approval of Celebrex?
A. I am aware of the studies that were supported in approval of Celebrex, yes.
Q. And do you -- is it your opinion, Dr. Graham,

that the COX-2 hypothesis had not been confirmed by the study results?
A. The study results primarily asked whether Celebrex was an effective NSAID, safe and effective NSAID within the framework of other NSAIDs; and it proved that.
Q. And that was -- you agree with me that was no longer as against the other NSAIDs, a hypothesis, by the time the FDA approved Celebrex?
A. Well, it wasn't a COX-2 hypothesis. It's an NSAID hypothesis.
Q. I see.
A. I mean similar data and similar endoscopic studies were done with your -- the drug we just talked about before, Relafen --
Q. Yeah.
A. -- showing it doesn't cause as much damage, et cetera, all the same kinds of studies. It was done with other NSAIDs, and that just showed it was a safe NSAID.
And the FDA said there's a CLASS label and you get the CLASS label that says "bleeding, perforation, obstruction," serious problems associated with NSAIDs. And if the COX-2 hypothesis is really true, then, you can get that label removed.

Q. There's a lot in that answer that we need to unpack. So I want to kind of go back to my question, which is -- and I think you answered it -- but you would agree with me that Celebrex's relative safety, GI safety against other traditional NSAIDs, that that had been proven before the FDA approved Celebrex for marketing in the United States?
MR. SAHAM: Objection, form, misstates prior testimony, and asked and answered.
A. I think your answer had too many dependent parts to it. They showed that if you brought another NSAID out, let's say a traditional NSAID, and you can get approval for that traditional NSAID because it is an effective NSAID and it doesn't cause any more adverse effects than other NSAIDs, so the FDA is going to approve it. I mean, they've got a model for that. You just go down the blanks. And Celebrex proved to be as effective as other NSAIDs, no better.
Q. You keep focusing on efficacy. I'm asking questions about safety.
So, we'll go back to my question: Do you agree with me by the time that FDA approved Celebrex that the studies that had been done comparing Celebrex against traditional NSAIDs had proven Celebrex had a relative GI safety advantage over those traditional

NSAIDs?
MR. SAHAM: Objection to form.
A. Safety is measured -- first of all, safety is measured by "how." I mean, are we measuring it for renal flux, are we measuring it for hypertension, are we measuring it for allergies and skin lesions, are we it measuring for endoscopic ulceration, are we measuring against Relafen, which no one's ever beaten, which is a traditional NSAID, what NSAID, what dose, et cetera.
You know, what was done is they show that if you took high doses of the really toxic -- gastro-toxic NSAIDs that you got fewer endoscopic ulcers, which have no known clinical relevance with this drug, the same as you got with Relafen. So I don't think that your answer's really factual.
I think the answer is: They got approval for another NSAID and the FDA left them with the same claim, that they have to -- that it has to have the CLASS claim as all other NSAIDs for safety, which is perforation, obstruction, bleeding.
Q. (BY MR. DOUGHERTY) My question, Doctor, was focused specifically on GI safety. So I'm not sure why your answer contained a lot of other things, but let me ask it again:
Do you agree with me that prior to the

approval of Celebrex by the FDA for marketing in the United States that it had been proven that Celebrex had a relative GI safety advantage over traditional NSAIDs?
MR. SAHAM: Objection, asked and answered.
A. No.
Q. (BY MR. DOUGHERTY) You disagree with that statement?
A. That broad statement, yes --
Q. Okay.
A. -- and I gave you the disclaimers that go around that statement, dosing, drug, et cetera, et cetera.
Q. On the endoscopy data -- and assume for purposes of this question and I know that you've got some opinions here about the utility of the endoscopic data -- but just assume for purpose of my question that the endoscopy data is useful data. You would agree with me that prior to the FDA approving Celebrex for marketing in the United States that it had been proven on the basis of the endoscopy data that Celebrex had a GI safety advantage over traditional NSAIDs?
MR. SAHAM: Objection, form, foundation, incomplete hypothetical.
A. No. I mean, you see, your question is "traditional NSAIDs." So if you said it's better than high dose Naproxen, I'm saying "Okay. It causes fewer

ulcers than high dose Naproxen." But all NSAIDs, including in the FDA claim said lowest dose, shortest time. So which NSAID, what dose, what duration?

(Discussion off the record.)

MR. SAHAM: Do you want to take a break?

THE WITNESS: No, I'm fine.

MR. SAHAM: Okay. Just let us know if you want to take a break, go to the bathroom or whatnot.

(Discussion off the record.)

Q. (BY MR. DOUGHERTY) Let me try it another way, Dr. Graham: Do you agree with me that the endoscopy studies showed that patients taking Celebrex had a substantially lower risk of ulcers detected by endoscopy compared to other patients who took other NSAIDs?

A. No --

Q. Okay.

A. -- when others that took specific NSAIDs at specific doses.

Q. Okay. Did you know that the statement I just read to you, Dr. Graham, is from the FDA?

A. It doesn't make any difference. It doesn't change the truth.

Q. Do you believe that -- let's take a step back here, Dr. Graham, and let's talk about the totality of the evidence on Celebrex. Are you familiar with the

totality of the GI safety data on Celebrex, as you sit here today?

MR. SAHAM: Objection to form.

A. I could never be aware of the totality of anything.

Q. (BY MR. DOUGHERTY) Do you intend to offer any opinions in this case that Celebrex does not have a GI safety advantage over traditional NSAIDs?

A. For that broad question -- I mean the answer that you just gave me for all traditional NSAIDs of all doses of all types, I would say that is not a factual statement.

Q. I'm going to ask the reporter to read back my question, because I think you may be anticipating something in my question that actually isn't there. So I'm going to have her read it back. And if you could just focus on what I've asked, that would be great.

(Question read back for the record.)

MR. SAHAM: I'd object to asked and answered and I'd ask you to read the answer back as well, since this is an identical question.

MR. DOUGHERTY: No, this is my deposition. We're not reading the answer back. I'll ask it again.

Q. (BY MR. DOUGHERTY) Do you intend to offer any opinions in this case, Dr. Graham, that Celebrex does

not offer a GI safety advantage over traditional NSAIDs?

MR. SAHAM: Objection, asked and answered.

A. And, again, I think that the concept of traditional NSAIDs is a very broad concept and there are many drugs and there are many doses; and there are drugs and doses for which there is no advantage of one drug over another.

In fact, all of the drugs, when they came out, even ibuprofen, did endoscopic studies to show they were safer and had an advantage over other drugs; and you can choose a dose and a duration and you can prove that.

The best one that I talk about that's in some of my papers was sulindac, which doesn't cause damage in endoscopic studies. It doesn't cause damage. So if you did that same model, it would look better than Celebrex.

Q. (BY MR. DOUGHERTY) Doctor, the opinion that I asked you about doesn't appear anywhere in your report, so I'm going to ask my question again.

A. It does appear in my report. I talk about doses and I talk about how one games a system in my report and the importance of dosing and -- in interpreting data.

Q. Okay. I'm actually not asking about dosing, Dr. Graham. I'm --

A. You are asking about dosing. When you tell me about traditional NSAIDs, dosing is the key element to safety.

Q. Let me try it another way, Dr. Graham, because maybe you and I can find common ground. You'll have plenty a chance to say what you want to say, but I also have a right to ask questions. And I'm assuming that --

A. Absolutely. I'm enjoying your questions.

Q. -- as a former Army officer, you actually feel duty-bound to answer questions that are put to you straight, right?

A. Absolutely.

Q. Okay. Are you offering any opinions in this matter that Celebrex is not safer than traditional NSAIDs?

A. I know of no data that it's safer than traditional NSAIDs.

Q. My question, though, is: Are you offering opinions in this case -- are you going to get to trial and say "Celebrex is not safer than traditional NSAIDs"?

MR. SAHAM: Objection, asked and answered, calls for a legal conclusion; but you can answer.

A. The data -- when one asked the question for outcome, bleeding, perforation, obstruction, compared to traditional NSAIDs, it proved not to be safer.

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Q. (BY MR. DOUGHERTY) Is that the extent of the opinions you're going to offer on that question?
A. No, that was the answer to your question.
Q. Okay. I guess I'm trying to figure out, Dr. Graham, whether you've actually done the work necessary to offer an opinion on whether the evidence -- the total evidence on Celebrex shows that it has a superior GI safety profile to traditional NSAIDs. Have you done that work necessary to offer that kind of an opinion?
MR. SAHAM: Objection to form.
A. I don't understand what the work would consist of.
Q. (BY MR. DOUGHERTY) How about reviewing all the clinical trial data involving Celebrex and focusing specifically on GI outcomes, have you done that as part of your assignment in this case?
MR. SAHAM: Objection, vague as to time.
A. The important GI outcome are perforations, bleeding, and obstruction.
Q. (BY MR. DOUGHERTY) Are you offering any opinions in this case -- all right. I appreciate that, but that's not really my question.
Are you offering any opinions in this case related to the results of the Success trial?

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A. Say again.
Q. Are you offering any opinions in this case regarding the results of the Success trial?
A. Which is -- well, do you want to describe the Success trial to me?
Q. Have you ever heard of the Success trial?
A. I've heard the name.
Q. Do you know what it is?
A. I can't give you details.
Q. Would it be fair to say, then, you're not going to be offering opinions about the Success trial, if you don't know what it is?
A. I don't know the details.
Q. What about the CONDOR study, are you going to offer any opinions in this case about the results of the CONDOR study?
A. There are two kinds of studies that are done and -- basically -- two basic kinds of studies. There are marketing studies which are designed to get a marketing advantage that are, if you like biased in many ways; and most of the trials, the big names, are marketing studies and don't address the question of safety.
So if you ask me about the safety issues in a marketing study, then I can easily have opinions. But

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I don't normally get involved in those kinds of studies because they really have -- they're really not scientific studies. They're marketing studies.
Q. Are you done with your ques- -- are you done with your answer?
A. Yes.
Q. What's the CONDOR trial?
A. The CONDOR trial was a big study to look at, among other things, hematocrit changes.
Q. And did you review the results of the CONDOR trial as part of your assignment in this case?
A. No.
Q. Do you mention the CONDOR trial anywhere in your report?
A. No.
Q. Do you intend to --
A. I do actually mention the CONDOR trial, if you like, in part of my report indirectly.
Q. Are you going to testify at the trial in this matter about what the results of the CONDOR trial showed with respect to Celebrex's GI profile?
A. I wasn't planning on it. I mean, to me, it was a marketing study of marketing value only.
Q. Have you looked at the minute analysis done for Celebrex on the question of GI safety?

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A. There have been a number of minute analyses done about GI safety of NSAIDs.
Q. Yes. Are you -- did you -- are you going to testify about those results in the trial of this case?
MR. SAHAM: Objection, calls for a legal conclusion.
A. I'm going to testifying about what people -- questions people ask me. And I'm not planning on that. That is not in my report.
Q. (BY MR. DOUGHERTY) So, you don't have any current plans to testify about those analyses?
A. I do not.
Q. Do you know a Francis Chan?
A. Yes.
Q. Is he a friend of yours?
A. A friend of mine, yes.
Q. Is he a good scientist?
A. Good man.
Q. Can you trust him?
A. Huh?
Q. Do you trust him?
A. As much as I trust other people.
Q. Comparing Mr. Saham to me, where do we come out on that scale?
A. Much higher.

Q. So, I mean, do you think that -- have you reviewed the results of the work that he's done on Celebrex?
A. Yes.
Q. And do you think he did good work?
A. Well, he has a very good research unit in Hong Kong.
Q. Have you re- -- do you question the validity of the conclusions that he's researched about his work researching Celebrex?
MR. SAHAM: Objection, form, foundation.
A. Which conclusions?
Q. (BY MR. DOUGHERTY) Do you even know what his conclusions are?
MR. SAHAM: Objection, form, foundation.
Q. (BY MR. DOUGHERTY) You see, here's where we're getting a disconnect. You either know the stuff and you have an opinion about it or you know it and you don't have an opinion about it or you don't know about it?
A. I know --
MR. SAHAM: Wait, Doctor. Objection, form. I mean, I'm not sure that that's a question. It's a speech.
Q. (BY MR. DOUGHERTY) So, I'll ask my question again: Are you aware of his work relating to Celebrex

and the conclusion that he's drawn regarding Celebrex?
A. I suspect that I'm more aware of his work and his conclusions than you are.
Q. Does that make you feel better? Can you --
A. No, no, but it might --
Q. Can you answer my question now?
MR. SAHAM: Well, your question is compound, for one.
A. Let's take his trial where he gave Celebrex or Diclofenac and PPI to high risk patients and published in the New England Journal, where he showed that there was no advantage to Celebrex. The patients re-bled at an unacceptably high rate on Celebrex.
So what would be the conclusion that I should take from that for Dr. Chan, the hypothesis that if they put a patient in high risk who had bled from an ulcer on Celebrex, he would have a safer NSAID. The answer was he did not. It was a very disappointing result. Now, which one do you want me to use?
Q. (BY MR. DOUGHERTY) Do you intend to testify about any of his work at the trial of this case?
MR. SAHAM: Objection, calls for a legal conclusion.
Q. (BY MR. DOUGHERTY) Dr. Graham, you can answer my question.

A. I don't specifically plan to testify regarding his work at the trial.
Q. You talk about things being hypothesis generating. Are you using that term and distinction to the term that you use in your report, which I think is "proven"? Are you distinguishing between something being proven and something being hypothesis generating?
A. In general, yes.
Q. And when you talk about something being proven, can you just define for us what you mean by "proven"? What are the criteria that you use?
A. In the context of a clinical trial, one makes a null hypothesis and states clearly that they hypothesize that A will be the same as B. And, then, they do a randomized control trial, randomizing for all the relevant factors; and they finish their study and they show that either A was different than B or A and B were not different.
If A and B are different, then by convention you have proven that within some statistical predetermined range. So that would be how you prove something.
Now, the hypothesis generating is data that already exists in the trial. Patients are entered and it turned out for some reason that there are more

red-headed ladies than brown-headed ladies and they have a different outcome; and that is not proven. That is an outcome of the study that was, if you don't mind, might likely be pre-determined by the population entered and, therefore, generates the hypothesis that red-headed ladies and brown-headed ladies have different outcomes. It has to be tested in a randomized -- another prospective randomized controlled trial.
Q. So, is it your testimony that -- in terms of clinical trials -- that it if you don't meet the primary endpoint, if the null hypothesis, for example, is not rejected, that all the other results from that trial are simply hypothesis generating?
A. Generally, that pretty is much the case. There are some waffling examples, but generally that's the case.
Q. Give me some waffling examples.
A. Well, the question you would have about the data would be "it depends somewhat on the magnitude of the difference you find and whether it's biologically plausible." But even then -- even then, most often they would need to be tested. There are many, many examples of data that pop out in a trial that actually get focused on by the authors that subsequent trials prove that it was wrong. In fact, it went in an entirely

wrong direction.
Q. And the contrary is also true, there are things that people focus on that have subsequently been proven to be true, correct?
A. That's why you have to do the studies.
Q. The conclusions that you reached about the VIGOR trial in the paper that you published with Dr. Jewel, are the results that you present there proven or simply hypothesis generating using the dichotomy that you just described?
A. More likely, they're on the proven side in that -- in that that the area that was listed as an important potential problem before they did a study and they had designed how they would analyze it and they fudged how they analyzed it; because it showed, if you like, a statistical significant difference and that they had planned on examining before the studies so that at least it would change the conclusions or how one dealt with the conclusions. And this was, again, picked up by one of the reviewers and not handled appropriately by Merck.
Q. So, we're taking your dichotomy between something being proven in a clinical trial and data that simply what you call "hypothesis generating" and you've explained that dichotomy to me.

And, then, we're now shifting gears and talking about the results that you present in your Vioxx paper that you co-authored with another plaintiffs' expert in this case, Dr. Jewel, and you said that you believe the conclusions that you reached in that paper were more on the proven side. Did I understand that correctly?
MR. SAHAM: Objection to the form of the question.
Q. (BY MR. DOUGHERTY) Is that your testimony?
A. That's what I said.
Q. Does that mean that there's some sliding scale between "proven" and "hypothesis generating" and that you put yourself closer to proven in your Vioxx paper?
A. There -- everything we do in life has got some gray. And when you start like they did by defining the parameters that you think will influence the outcome and that say you're going to do subgroup analysis for them to see if they determine or if they affect the outcome and, then, you fudge that analysis, that's what we said they did.
Q. You said that you believe that your Vioxx paper was more on the proven side rather than the hypothesis generating side because what you were studying had been planned -- that there had been a plan in the clinical

trial to examine those events and that plan existed before the data was unblinded. Did I -- is that what slides it towards the proven side of the scale?
MR. SAHAM: Objection to form.
A. Not exactly.
Q. (BY MR. DOUGHERTY) Okay. Can you just give us the factors that are influencing your opinion that your own work in the Vioxx paper is more towards proven rather than hypothesis generating?
A. The Vioxx paper, the -- it was known that corticosteroid users had higher risks.
Q. Okay. So --
MR. SAHAM: Are you going to let him finish his answer?
Q. (BY MR. DOUGHERTY) okay. So we're going to -- we're going to have to change the tape in a second, so I just --
MR. SAHAM: Well, no. Are you done with his answer?
MR. DOUGHERTY: No, he's not done with his answer. He's got more to go, but I want to just take these one at a time because the tape is going to have to cut off.
Q. (BY MR. DOUGHERTY) So, the first thing that you said --

MR. SAHAM: Are you withdrawing the prior question, because he didn't finish his answer?
MR. DOUGHERTY: No, no, he's going to give me some factors. I'm just getting clarification.
MR. SAHAM: Well, he's not done answering this last question then.
Q. (BY MR. DOUGHERTY) One of the factors you said, Dr. Graham, you said that there was information about the relationship between corticosteroid users and the events that you were studying and that information predated the trial; is that --
A. Right.
Q. Okay. So preexisting information is one factor that would slide it more towards "proven" rather than "hypothesis generating"; is that right?
MR. SAHAM: Objection, form.
A. I -- maybe.
Q. (BY MR. DOUGHERTY) Okay. What are the other factors?
A. No. We're discussing the Vioxx trial, right? And, so, this was known and, so, they said "This is known and this could influence our outcome. And, so, we are going to -- a part of our analysis we are going to look at this question. We're not going to subgroup now. We're going to look at this question. And there's a

term "interaction" and we're going to look for interaction to see if there is an interaction and does that affect our data.

And the answer was: Yes, there was an interaction. It was significant and all their events were in that one subgroup, 100 percent of them, basically.

So, they were offered, basically, by the reviewer to say they didn't -- they didn't want to have a claim that said it's only good in patients who take -- that had rheumatoid arthritis and take steroids. And that was -- they could have -- they had that data from their trial.

Q. So, again, what we're focused on here is why you believed that your and Dr. Jewel's analysis of the VIGOR results are more "proven" than they are "hypothesis generating"; and I think you've given me at least two factors. One is that there was some preexisting information or it was known that there could be an association. And I think the second thing you said is the trial was designed to look for that interaction. Is that fair?

A. Right.

Q. Any other factors that move your Vioxx paper towards the "proven" side of the scale rather than the

"hypothesis generating" side?

A. We did the analysis that they should have done.

MR. DOUGHERTY: Okay. We're going to have to change the tape. This might be a good time to take a quick break.

THE VIDEOGRAPHER: This is now the end of tape No. 1 of the deposition of David Graham. We're off the record at, approximately, 10:36.

(Whereupon, a recess was taken from 10:36 a.m. to 11:02 a.m.)

THE VIDEOGRAPHER: We're now back on the record with tape No. 2 of the deposition of Dr. David Graham. The time is, approximately, 11:03.

Q. (BY MR. DOUGHERTY) Dr. Graham, would you agree with me that subgroup analyses of data coming from a clinical trial can be clinically important?

A. Of course, anything can be clinically important. It's not hard to know that. It's hard to know that prospectively.

Q. So, the answer to my question is "it depends"?

A. It depends.

Q. Okay. The subgroup analyses that you presented in your Vioxx paper with Dr. Jewel, did you believe that that information was clinically important?

A. Again, what we did, basically, was repeat the

analysis that they had planned to do, but do it correctly. So, I mean, it wasn't a new analysis. It was the analysis that they had described, but that they had, if you like, fudged part of the data.

Q. It was a subgroup analysis, though, wasn't it, Dr. Graham?

A. Part of it was a subgroup analysis, yes.

Q. And do you believe that the information that you and Dr. Jewel presented in your paper was clinically important?

A. Well, it showed that the understanding of the outcome of the trial was different than had been presented.

Q. That was your opinion?

A. Those are what the data, at least as we analyzed them, showed, yes.

Q. Okay. And, again, do you think it was important for people to know that information?

A. I think it was important to know that the study results were different than had been presented.

Q. And that's why you published those results?

A. Yes.

Q. And did you get paid to do that work?

A. No.

Q. Did that work come out of the your Vioxx

engagement?

A. I mean, it came out of the -- having done the Vioxx study the same way with, hopefully, that these data will be released by the judge and we can write up these data.

Q. What data are those, Dr. Graham?

A. The CLASS trial.

Q. You don't believe those data have been made available already?

A. The data that comes out in the various depositions has not been made available. I mean, the internal documents about what people were thinking and doing, et cetera, has not been made available. If it is, then we'll just write up now.

Q. Do you some plan to write up as part of the assignment in this case some article?

A. If possible, yes.

Q. And who have you had those discussions with, Dr. Graham?

A. No one. I mean, you know, this is what we do in academic medicine, is "we write."

Q. Well, that's not exactly what you're describing here. You're describing using an assignment as an expert for plaintiffs' lawyers and to use the information that you get as part of that assignment to

write some article that you want to get published somewhere?
MR. SAHAM: Objection, form.
Q. (BY MR. DOUGHERTY) Isn't that what you just described?
A. Yeah, that's -- I mean, I think that the truth is the truth. And if you think that the data are incorrect and that they were -- then someone should set the record straight.
Q. So that's your current intention, is to take the information you've gained as part of this assignment and write an article?
MR. SAHAM: Objection, misstates prior testimony.
A. My objective -- my intention would be if the data are all released by the judge, is to write up about what the CLASS trial really showed and what the analysis really was or should have been.
Q. (BY MR. DOUGHERTY) And, so, now I'm going to come back to my original question because in your answer you gave me some reference to emails.
Do you believe that the CLASS study data has not been released already to the public?
MR. SAHAM: Objection, form, foundation, vague as to "CLASS data."

A. Do I think it's not been released? I think that the JAMA article, understanding of the background, et cetera, the JAMA article is not the generally known among clinicians -- among physicians, right.
Q. (BY MR. DOUGHERTY) That's really not my question. You said the background of the JAMA article. You keep talking about the JAMA article. I'm talking about the CLASS data, because -- maybe we have a disconnect here.
Do you not know, Dr. Graham, that the entirety of the CLASS study data has been in the public domain for quite awhile?
MR. SAHAM: Objection, form, foundation --
Q. (BY MR. DOUGHERTY) Did you not know that?
MR. SAHAM: -- vague.
A. I know that the CLASS data has been in the public domain for a long time.
Q. (BY MR. DOUGHERTY) So, what you want to publish is not something about the CLASS data. You want to publish something about -- that would include emails that have been produced by the Defendants in this litigation? That's what you want your article to include?
A. It would, yes.
Q. And have you talked with the Plaintiffs' lawyers

about that intention?
A. I mean, I've mentioned it to them.
Q. And when did you first mention that to them?
A. Well, I have no idea.
Q. When were you first contacted about being an expert in this litigation?
A. Maybe a month before this was written (witness pointing to Exhibit No. 1054).
Q. And who contacted you?
A. Somebody from their office.
Q. Had you heard about this litigation before that first contact?
A. I don't think so.
Q. Have you talked with Dr. Jewel about this case?
A. Not specifically.
Q. Have you talked with anyone about this case, other than the Plaintiffs' lawyers?
A. No.
Q. Have you shared any information that's been made available to you in this case with anyone?
A. No.
Q. Where is that information currently stored, Dr. Graham?
A. You mean the documents?
Q. The documents that have been provided to you

under protective order in this case, where are they?
A. They are in a pile on a chair in my home.
Q. And has anybody other than you seen those documents?
A. No.
Q. Have you spoken with Dr. Abramson about this case?
A. Never.
Q. Have you ever met him?
A. I -- once or twice in the past, yes, not -- except just in passing.
Q. You mean when you were both acting as experts for plaintiffs in other cases?
A. No.
Q. Did you know that he's acted as an expert for plaintiffs' lawyers in some of the cases that you have?
A. I had heard his name.
Q. But you didn't meet him in connection with that?
A. No.
Q. Have you performed any independent analysis of the CLASS data, Dr. Graham?
A. No.
Q. What was your assignment in this case?
A. My assignment was to read what Dr. Wang had written and to write a rebuttal.

Q. Okay. So, you're not going to offer any opinions in this case based upon your own analysis of the CLASS data; is that correct?
MR. SAHAM: Objection to form, foundation.
A. I'll answer the questions that people ask me.
Q. (BY MR. DOUGHERTY) How about answering the question that I just asked you?
Q. Well, I --
MR. SAHAM: He just did. Objection to form.
A. I just thought I had.
Q. (BY MR. DOUGHERTY) No, I asked you whether you intended to testify in this case about any analysis that you, yourself, performed of the CLASS data?
A. No.
Q. Because you haven't -- you haven't analyzed those data yet; is that fair?
A. I have not done a specific analysis of the CLASS data.
Q. You're waiting for this assignment to be over for you to do that, to write this article that you want to publish?
MR. SAHAM: Objection, form, foundation.
A. I'm not going to waste a bunch of time if the judge keeps it all locked up.
Q. (BY MR. DOUGHERTY) Do you intend to offer any

opinions in this case about the design of the CLASS trial?
A. No.
Q. So, therefore, we will not hear you at trial testify about criticisms of the CLASS trial design; is that fair?
A. My assignment was Dr. Wang and his rebuttal.
Q. So the answer to my question is you're not going to testify --
A. I don't plan to.
Q. -- about the design of the trial?
A. (Witness shakes head.)
Q. Okay. And you're familiar with the VIGOR trial, are you not?
A. Yes.
Q. And do you believe that the endpoint selected for the VIGOR trial was clinically relevant?
A. I think the endpoint of bleeding, perforation, obstruction were clinically relevant.
Q. What was the endpoint for the VIGOR trial, Dr. Graham?
A. Well, VIGOR had broader endpoints. They were -- they like ulcers; but the main endpoint is bleeding, perforation, obstruction.
Q. Your testimony is, is that the main endpoint for

the VIGOR trial was bleeding --
A. The main endpoint for -- as the FDA decided and clinically, I believe, it would be bleeding, perforation, obstruction.
Q. But that's not actually what the protocol specifies as the primary endpoint?
A. That's a different question.
Q. So, let's stick with that question. What was the primary endpoint of the VIGOR trial?
A. I cannot tell you exactly what it was. We can look it up.
Q. Do you agree that it was -- included events other than bleeding, perforations, and obstructions?
A. It included other events that they looked at.
Q. They looked at a lot of events, Dr. Graham?
A. They did.
Q. And I'm really just trying to drill down on the primary endpoint; and if you don't know what the primary endpoint is of the VIGOR trial, then just say you don't know.
A. I don't know exactly what their primary endpoint was.
Q. So, you can't answer any questions about whether the primary endpoint in the VIGOR trial was clinically important because you don't know what that primary

endpoint is; is that fair?
MR. SAHAM: Objection to form, misstates prior testimony, assumes facts not in evidence.
Q. (BY MR. DOUGHERTY) You can answer the question, Dr. Graham.
A. I don't think that's fair.
Q. What, the question?
A. Your answer -- your question was "is that fair" the -- your summary.
Q. I'll come back. I've been trying to get to the same thing for a couple of minutes here.
Since you don't know the primary endpoint of the VIGOR trial, you can express no opinion, Doctor, about whether the primary endpoint was clinically important or not?
MR. SAHAM: Objection to form, misstates prior testimony, assumes facts not in evidence.
A. If you'll define what endpoint you want to discuss, then we can discuss whether I think that's clinically relevant.
Q. (BY MR. DOUGHERTY) But you can't answer that today?
A. Not today.
Q. Okay. There must have been a point at which you recalled the primary endpoint of the VIGOR trial because

you wrote on article on it, right?
A. Absolutely.
Q. Would looking at that article help refresh your memory about what the primarily endpoint of the VIGOR trial was?
A. It might.
Q. We'll get that and come back.
Do you believe that the only clinically important information in either the VIGOR trial or the CLASS trial were the results on perforations, obstructions, and bleeding?
A. Clinically important information is an extraordinarily broad term. The hypothesis that COX-2 inhibitors would be somehow different than traditional NSAIDs was that they would be void of or remarkably less of these events. So that is the important scientific question.
Now many, many clinical questions could come out that would be of interest and some of them might even be important.
Q. Are you finished?
A. Finished.
Q. So what are the other things that might be clinically important, other than perforations, bleeding, and obstructions?

A. Well, they're interested in, for example, cardiovascular events came out to be a very important question.
Q. I'm talking about all GI safety trials involving COX-2's. That's the frame that I'm using for my question. And, so, will you accept that frame for purposes of my question?
MR. SAHAM: Objection, form, foundation assumes facts not in evidence.
A. Yes.
Q. (BY MR. DOUGHERTY) Okay. So, is it your opinion, Dr. Graham, that the only clinically important information in all COX-2 GI safety trials is the results on perforations, bleeding, and obstructions?
MR. SAHAM: Objection to form, misstates prior testimony.
A. Obviously, there could be a tremendous amount of potentially clinically important information come out any trial.
Q. (BY MR. DOUGHERTY) Why don't you list for us the clinically important information that would come out of GI safety trials involving COX-2's, other than perforations, bleeding, and obstruction and, again, focusing on the GI safety question?
MR. SAHAM: Object to the form of the

question.
A. That are COX-2-specific or that differentiate COX-2's from other NSAIDs?
Q. (BY MR. DOUGHERTY) Yes, sir.
A. That's about it.
Q. Perforations, bleeds, and obstructions, that's about it?
A. That's about it.
Q. So, is it your opinion, then, that there is really no utility to any clinical trial investigating the question of GI safety involving COX-2's that doesn't have as its primary endpoint perforations, obstructions, and bleeding?
A. That would differentiate COX-2's from traditional NSAIDs?
Q. Yes, sir.
A. Maybe you can come up with some examples, but I can't think of one at the moment.
Q. Let's take a look at what I'm going to show you has previously been marked in this litigation as Exhibit 1016. I promised you we'd pull out your and Dr. Jewel's article.
Dr. Graham, is this the article that you published after your assignment as a plaintiffs' expert in the Vioxx litigation?

A. Yes.
Q. And with reference to the article now, Dr. Graham, can you remind yourself with reference to your own work what the primary endpoint was in VIGOR?
A. I don't know if we stated it, like I stated here, that whether Rofecoxib was less likely to cause clinically important ulcer complications than traditional NSAIDs was specifically evaluated in the VIGOR study.
Q. What page are you on there, Dr. Graham?
A. 359.
Q. And where on that page where the reader of this article find the primary endpoint of VIGOR?
A. I don't know if we listed the primary endpoint, but it says here it included symptomatic ulcers -- and I don't think -- I don't know if we listed actually the primary endpoint as listed in the protocol.
Q. Dr. Graham, if I could take -- turn your attention to that page that you're on, 359, and there's a heading there that says "Rofecoxib Compared with TNSAIDS." Do you see that heading?
A. Right, right. I just read that to you.
Q. That first paragraph down -- I'm just going to quote to you what you've written here, quote: "The primary endpoint was confirmed clinical upper GI events

(gastroduodenal perforation or obstruction, upper GI bleeding and symptomatic gastroduodenal ulcers)."
A. Okay. I found it.
Q. So, was that the primary endpoint of the VIGOR?
A. That presumably was.
Q. Okay. And was that a -- was that primary endpoint of clinical importance?
A. I mean, obviously, it's of importance. The least important one that we discussed that to was symptomatic gastroduodenal ulcers. We discussed that that is an inconvenience. The others are life-threatening.
Q. Would you agree with me that this combined endpoint of the VIGOR trial was capturing clinically important information?
A. It could. It's also one that was very "gameable," that you could capture clinically unimportant information and put it into there, which is one of the reasons that we felt that it was a -- not a good endpoint because it was clinically not interpretable as being meaningful.
Q. Doctor, are you trying to tell me that you're criticizing the primary endpoint in this article?
MR. SAHAM: Objection to form.
A. I criticize the inclusion of that endpoint.
Q. (BY MR. DOUGHERTY) Do you criticize the

selection of the VIGOR primary endpoint in this article?
A. I would criticize that particular endpoint as being clinically unequivocal unimportant.
Q. So, if you had designed the VIGOR trial, you would not have included symptomatic gastroduodenal ulcers?
A. Correct.
Q. And do you know why the FDA accepted that combined endpoint for the VIGOR trial?
A. No.
Q. I'm sorry. Did you answer?
A. I answered "no." Yes, I answered "no."
Q. Okay. Thank you.
Do you remember giving testimony in that case, Dr. Graham?
MR. SAHAM: Objection to form, vague.
Q. (BY MR. DOUGHERTY) In the Vioxx case? I'm sorry.
MR. DOUGHERTY: Thank you, Scott.
A. I remember giving testimony.
Q. (BY MR. DOUGHERTY) And you recall, Dr. Graham, that when you gave testimony in the Vioxx trial you were under oath, right?
A. I thought I was under oath now.
Q. Well, I was just going to say you're under oath

now; but you were under oath when you gave the Vioxx testimony, correct?
A. Right.
Q. And did you tell the truth when you gave that testimony?
A. Best I could.
Q. Did you give that testimony before you were hired as an expert in this case?
A. I gave that testimony before I was hired as an expert in this case.
Q. I'm going to read you a portion of the testimony that you gave in the Vioxx case, Dr. Graham; and I want to see whether you stand by what you said or whether your views have changed.
MR. SAHAM: John, I object, if you're going to read some testimony. I think you could show it to him and make sure it's being read correctly, because he doesn't have the foundation if it's not.
MR. DOUGHERTY: I can do that, but let me just -- let me just read what we've got here.
Q. (BY MR. DOUGHERTY) Let me withdraw the question. We'll come back to it. I need to do a foundational piece that I haven't done yet. So I'm going to withdraw that question and then we'll come back. I'm sorry about that.

A. No problem.
Q. We're going to come back to that after a break because I need to -- I didn't have the full document in front of me.
A. As you wish.
Q. Thank you, sir.
Okay. So, your view is that the VIGOR -- your view now is that the VIGOR trial primary endpoint by including symptomatic gastroduodenal ulcers made that primary endpoint less clinically relevant; is that fair to say?
MR. SAHAM: Objection to form.
A. It made it less clinically relevant. That was an ambiguous primary endpoint.
Q. (BY MR. DOUGHERTY) And you would have preferred just simply to see the perforations, obstructions, and bleeding be the primary endpoint?
A. I would have preferred that.
Q. And in -- how long have you been practicing medicine?
A. Since 1966.
Q. And you've been treating patients pretty much since then?
A. Yes.
Q. And in this last year, how many patients in your

practice do you see, just on an average year?
A. I don't know, not that many, maybe 3 or 400.
Q. In the general population, Dr. Graham, do you know how often someone experiences either perforation, obstruction or bleed?
A. In the general population?
Q. Correct.
A. It's, in part, age-related so that it would be dependent on age. For example, 80-year-olds, it would probably be about 2 percent per year, maybe 3.
Q. And they're at higher risk for those?
A. They're at higher risk.
Q. So for a younger population, the rate's going to be lower, correct?
A. Remarkably lower.
Q. And, in fact, perforations and obstructions and bleeds are, thankfully, pretty rare events?
A. Rare events in the -- per patient, but not per population. We have about half a million bleeds per year in America. So it's a big problem.
Q. Well, I'm not arguing whether it's a big problem. I'm actually asking you the question of how often do they occur in the general population as a percentage?
A. In the general population -- an average walking-talking general population, it's not very

common. It's less than 1 percent.
Q. And do you in your practice of medicine, do you routinely scope your patients -- and by "scope" I mean in upper endoscopy?
A. Well, I don't routinely do that anymore; but I did that until recently.
Q. And why did you stop?
A. I outgrew it.
Q. I see. Fair enough.
A. There are other people to do that busy work.
Q. How many endoscopies do you think you've performed in your career?
A. Tens of thousands.
Q. And do you perform those endoscopies -- well, when you will perform an endoscopy? Describe to me what a patient would present in order for you to go through the time and presumably the expense to the patient of doing an endoscopy?
A. Well, I'm frequently going to do that either because they have symptoms that suggests there's a problem -- and we're talking about upper gastrointestinal endoscopy.
Q. Correct.
A. Symptoms suggestive of something erroneous -- going wrong in the upper gastrointestinal tract, an

ulcer or whatnot, or because they have a complication, such as a bleed that would -- or something I want to treat specifically or that they did, swallowed something that I want to go remove. I mean lots of indications.
Q. Okay. So, let's kind of break that down. You have patients that present to you that either because of the blood work or because they're complaining of a dark stool or blood in the stool, you've got a blood loss issue, and that would be one motivation and a strong motivation for you to scope that patient; is that correct?
A. That would be one indication, yes.
Q. Okay. So let's take blood loss and put that off to the side, and let's put off to the side somebody that swallowed something or inhaled something or other reasons for you to go in and take a look and see what's down there.
Let's focus on people that are presenting to you with symptoms. What was your practice when you were doing endoscopies in evaluating whether a patient should go through the time and expense of an endoscopy based upon the symptoms that they were presenting? Just describe that for us.
A. Well, it's a -- you're dealing with a referral practice, primarily. So patients are often referred to

you from some other physician because they're concerned and they would like the patient to have a procedure for evaluation so that it's somewhat different than if it's your patients.
Q. I see.
A. But --
Q. And if you had gotten -- if I could just interrupt, if that's okay -- on a referral basis, if say a primary care physician sent somebody over for referral because they were concerned, they would ask you to do an endoscopy and they'd come to your office or whenever you would perform those. Is that fair?
A. That's fair.
Q. And would you refuse to do the endoscopy because you would second-guess the judgment of the referer?
A. Sometimes.
Q. Okay. When you -- so taking the referral piece out for a second and focusing on just when you would do it, so you weren't asked to do it, but you had to make the independent clinical judgment as to whether to scope, describe the kind of symptoms that would cause you to want to scope a patient.
A. Recurrent abdominal pain, weight loss or they could have classical symptoms of something. For example, they could have classical symptoms for

gastroesophageal reflux because I know what the diagnosis is, but I want to see if there's a complication present.

Remember gastroenterologists, that's what we do, is scope people. So, we think about it like shining a flashlight in a person's throat that has a sore throat and you just -- and I do almost all of mine unsedated. So it's just a quickie. "Did you have breakfast?"

"No."

"Let's take a quick look."

Q. All right. And how often when you would scope patients that were presenting with any kinds of GI symptoms, whether it be blood loss, abdominal pain, how often would the endoscopy procedure confirm the existence of some ulceration?

MR. SAHAM: Could you read that back?

(Question read back for the record.)

MR. SAHAM: Objection, form, compound.

A. That's an error-type question. For example, if you go back 30 years, 20 years when Helicobacter was common and ulcers were common, you would be pretty reliable about seeing that there's an ulcer. Today, it would be pretty infrequent.

Q. (BY MR. DOUGHERTY) How common was it, I mean, just as a percentage of the people that you scoped that

you would confirm they had an ulcer?

A. Oh, many of them had ulcers before. And, so, in that kind of patient, it'd probably be 50, 60, 70 percent.

Q. What about the ones you had not already documented the existence of an ulcer?

A. Today, it'd be less than 1 percent.

Q. And I'm not talking about today. I'm talking about, say, ten years ago?

A. Well, it still would still be a low percentage.

Q. And, yet, you would do the endoscopy just to make sure, correct?

A. Well, there's a lot of reasons to do the endoscopy, among which is we say to each patient "The benefit's not only from what you find, but that you didn't find"; because they're concerned often that they have cancer or something else.

Q. Okay. So -- just so that there's no ambiguity about this later, Dr. Graham, do you agree with me that endoscopies are an important tool for a gastroenterologist?

A. It's what we do.

Q. And you would agree with me that scoping a patient can confirm or rule out the existence of an ulcer?

A. It can.

Q. And, in fact, for a patient presenting symptoms of some kind of gastrointestinal distress, endoscopy is a common way to rather quickly confirm or rule out an ulcer as the contributing cause of those symptoms; is that fair?

A. It's frequently used that way in patients.

Q. And you don't want anybody misreading your opinions in this case as saying that you don't believe that endoscopies are an important tool for clinicians?

A. Endoscopy is an important tool for clinicians.

Q. And endoscopies are the quickest way for us to confirm clinically the existence of an ulcer, correct?

A. Absolutely.

Q. And you would agree with me that the rates of ulceration, to pick up on one of your previous answers, have gone down in recent years; is that correct?

A. The rates of ulcers as clinically significant problems has gone down over the years.

Q. And you attribute that to what, Dr. Graham?

A. I attribute that to getting rid of Helicobacter, primarily.

Q. Okay. And how do you as a gastroenterologist get rid of H. Pylori?

A. It's an infectious disease. You treat it with

antibiotics.

Q. Okay. And when did you first become a believer in treating H. Pylori with antibiotics?

A. When we had the data that it made a benefit, which would be in the late '80's.

Q. Okay. And do you believe that treating H. Pylori with antibiotics is the main reason that ulceration rates have gone down?

A. That and the widespread use of proton pump inhibitors.

Q. PPIs?

A. PPIs.

Q. Now, PPIs don't do anything to protect the lower GI tract; is that fair?

A. Well, we don't know that for sure; but that's what our belief is, yes.

Q. Okay. And you can have ulcerations in the lower GI tract, can you not?

A. Certainly.

Q. An endoscopy, the classical kind of upper GI endoscopy is not going to reveal those ulcers?

A. Not -- upper endoscopy is not going to reveal those ulcers.

Q. You could do a capsule study these days, right?

A. You could.

Q. And when did it become common to do capsule studies to detect ulcers in the lower GI tract?
A. Oh, in the last ten years.
Q. And you would agree with me that lower GI tract ulcers are as significant clinically as upper GI ulcers with respect to patient health?
A. Oh, I don't think I would agree with that.
Q. You don't -- you wouldn't agree with that?
A. No.
Q. Do NSAIDs have any effect on the lower GI tract, Dr. Graham?
A. They can have an effect on the entire GI tract.
Q. Okay. Do you -- and, so, taking a PPI with a traditional NSAID is not going to reduce your risk of having a lower GI tract ulceration; is that fair?
A. It shouldn't.
Q. And have there been advances in the last ten years in treating lower GI tract problems?
A. Probably not, I mean, beyond Misoprostol.
Q. If you have a patient that's presenting with blood loss and you scope that patient and you do not find an ulcer, is one of the things that's going through your mind as a treating physician the possibility of a lower gastrointestinal ulcer?
A. Of course.

Q. And you intervene as a physician at that point, do you not?
A. Say again.
Q. You intervene in the patient's care at that point, do you not?
A. I might.
Q. In fact, if a patient comes to you -- for example, if I walked into your office later today and I presented to you kind of classic gastrointestinal distress, would you treat me?
A. As we said before, if you walk into a gastroenterologist's office with symptoms, you're going to get endoscopy.
Q. Okay.
A. If you walk into your general practitioner's office with the same symptoms, you're probably not going to get endoscopy. You're probably going to get symptomatic therapy to see if it would respond or not.
Q. Okay. And what you're simply pointing out there is the tools available to a gastroenterologist are different than the tools available to a primary care physician?
A. Well, hopefully, most patients will go to their primary care physician and be triaged and so they won't get unnecessary procedures.

Q. And if a patient comes to you complaining of gastrointestinal distress and tells you that they're on an NSAID, would you advise them to stop taking the NSAID or to take a PPI to see whether or not that could alleviate their symptoms?
A. It depends on the patient, I mean, if it's a new patient or an old patient, et cetera, et cetera. Now when you get down to specific patients, then one does patient-specific therapy, so....
If you came to me from New York City and sat down, "I've got a severe discomfort and I'm taking a" -- and I say "Are you taking an NSAID," then I would probably evaluate you.
Q. And you would ask the question to a patient whether or not they're taking an NSAID, correct?
A. I would ask the question "What medicines are you taking," yes.
Q. And you would focus specifically in your list on NSAIDs because NSAIDs are known to have GI toxic effects, correct?
A. No, I wouldn't necessarily say that. I would ask them about all drugs, but that would be on my list aspirin and NSAIDs. Many people take aspirin, for example.
Q. Yeah. So the ordinary person, like the members

of the jury in this case, Dr. Graham, they likely believe that aspirin can burn a hole in your stomach. Would you want to dis-abuse them of that belief?
MR. SAHAM: Objection to form, foundation, assumes facts not in evidence.
A. Patients have lots of beliefs. I tend not to try and dis-abuse them of their beliefs.
Q. (BY MR. DOUGHERTY) But they would actually have a scientific and medical basis for believing that aspirin can cause an ulcer, correct?
MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.
Q. (BY MR. DOUGHERTY) Go ahead.
A. Aspirin can definitely cause ulcers.
Q. And so can ibuprofen, can it not?
A. Any NSAID.
Q. Naproxen?
A. Celebrex.
Q. Do you believe that the ulcer rates for Celebrex are equivalent to Naproxen and Diclofenac and ibuprofen?
A. Now, the analyses, when we get into murky water, because we're talking clinical ulcers and endoscopic ulcers and endoscopic ulcers are frequently not ulcers. They are frequently -- in fact, we used to code those in the studies as "ulcer for study purposes only." If we

had seen it clinically, we wouldn't have called it an "ulcer."

So, that's when you get into -- why I say the symptomatic ulcer are real problems; because, as I point out in my report and in my paper, that symptoms are very common in patients taking NSAIDs, ulcers aren't. Endoscopic ulcers are quite common. Clinical ulcers aren't. So many patients have symptoms and little -- what I call "ditzels," little things, that would meet the criteria for an endoscopic ulcer and be clinically thought to be or equated in the naive mind as a clinical condition of some known significance. And, so, this ambiguity has been used by Pharma greatly in their marketing.

Q. What have you done personally, Doctor, to inform the medical community about the opinion that you just expressed on the difference between symptomatic and clinical ulcers? What research have you done and published?

MR. SAHAM: Objection to form.

A. I've written a bunch of papers about that, even to the fact that I took the videotape used in one of the clinical trials and took off all the words so you couldn't read what they were calling it and sent it coded and blinded to Dr. Chan's group and had them look

at it and see if they agreed with what the clinician -- what the study wanted you to call "ulcers" and "not ulcers" and they're in very, very poor agreement.

Q. (BY MR. DOUGHERTY) What -- in the VIGOR trial, were patients scoped as a matter of routine in that trial?

A. The VIGOR trial was designed to encourage endoscopy. Every time the patient was communicated with by phone or any other way, they listed its symptoms. And any time they listed its symptoms, they encouraged endoscopy because presumably they knew that endoscopic ulcers were more common in the NSAIDs and that they would, therefore, bias the study towards more ulcers, more endoscopic ulcers in the NSAIDs versus Rofecoxib.

Q. Well, how would that help the Rofecoxib group?

A. Because they want to show they're different. So if they can increase the number, then in the non-Rofecoxib group, then they look better, even though it's clinically irrelevant.

Q. I need to explore that with you a little bit, Dr. Graham, because the trial designed for VIGOR did not differentiate. You say it was biased in favor of endoscopies, but that was across both treatment groups, right?

MR. SAHAM: Objection to form.

A. If you -- from the studies that they have done before at those doses, they knew that VIGOR, I mean, the COX-2, Rofecoxib, had a lower symptomatic rate than the other two drugs or at least ibuprofen. And they knew it had a lower endoscopic ulcer rate than ibuprofen, because ibuprofen is a topically toxic drug. And, so, therefore, they could predict that by chance they were going to identify more endoscopic ulcers in the traditional NSAID group than in the Rofecoxib group.

They're not dummies. So they knew and before they started the study that they could bias it. So they went out of their way to make sure they biased it as much as they could.

Q. (BY MR. DOUGHERTY) Who went out of their way?

A. The protocol.

Q. The protocol. How did a doctor who was -- you say was encouraged to scope -- that doctor had no idea what therapy the patient was taking, correct?

A. No, he didn't have any idea or she different have any idea.

Q. Right.

A. But they knew that they were more likely to have endoscopic ulcers and more likely to have symptoms; and so, therefore, they could have more endoscopic ulcers in their group, the comparator group.

Q. So, you're saying that because the prior studies of Vioxx had showed that NSAID patients would have more endoscopic and symptomatic ulcers on tradi- --

A. No, more symptoms and more endoscopic ulcers independently.

Q. Okay. So kind of breaking this down a little bit, the prior studies of Vioxx had shown that patients taking traditional NSAIDs would have more symptoms than patients on Vioxx; is that --

A. Right.

Q. -- is that what you're saying?

A. That's right.

Q. And you're saying that the data before VIGOR also showed that patients taking traditional NSAIDs would have more endoscopic ulcers than those taking Vioxx?

A. Yeah, independent of the symptoms, so that it's true, true and unrelated.

Q. Okay. So, it's your opinion, then, Doctor -- it must be your opinion -- that that those data that show NSAIDs users have more symptoms and more endoscopic ulcers than Vioxx users that that data must be accurate, correct?

MR. SAHAM: Objection to form --

A. From the studies they did --

MR. SAHAM: -- assumes facts not in

evidence.
A. -- with the doses they did, and the same holds for Celecoxib, that the "coxibs" with those doses, et cetera, caused fewer endoscopic ulcers and fewer symptoms.
Q. (BY MR. DOUGHERTY) So, do you believe that prior to the VIGOR trial that it had been proven that traditional NSAID users would have more symptoms than Vioxx users?
A. No, it had been shown that those NSAIDs at those doses -- remember when they did Rofecoxib, they found absolutely no difference. So when you say traditional NSAIDs, you must talk about drug and dose.
Q. Fair enough. Let me ask you a different way.
We know that Naproxen was the comparator arm in the VIGOR trial, correct?
A. Which is the most gastro-toxic of the drugs that we normally use.
Q. Okay. So, are you saying that it had been proven prior to the VIGOR trial that Naproxen users would have more symptoms and more endoscopic ulcers at the doses used in the VIGOR trial than those taking Vioxx, that that had been proven?
A. That was what the data showed. So they had allowed one to "game" the study.

Q. I want to stay with the "proven." So, do you believe that it had been proven as opposed to hypothesis generating?
A. Proven in the clinical endoscopic study.
Q. So, using the measures of just endoscopic ulcers and symptoms, you believe that even before the VIGOR trial had begun that it had been proven that Vioxx users had fewer endoscopic ulcers and fewer symptoms than Naproxen users. Is that fair?
A. At that dose, right.
Q. And -- now moving over to the CLASS trial, same questions: Do you believe that prior to the start of the CLASS trial it had been proven that Celecoxib was superior to either Diclofenac and ibuprofen using endoscopic ulcers and symptoms as the events?
A. I can't speak about Diclofenac. I mean, Naproxen at that dose -- I mean -- pardon me -- ibuprofen at that dose is, again, very gastro-toxic. So, I mean, you're taking the worst drug at the worst dose and for endoscopic ulcers and comparing it to your drug. And, so, that I could take ten other NSAIDs and show they were -- in fact, that all the other NSAIDs they came out proved they were better and safer and less symptomatic than ibuprofen by using the same kind of model --
Q. Right.

A. -- for symptomatic -- for endoscopic ulcers.
Q. Prior to the start of the CLASS trial -- so you can't offer any opinion on the data with respect to --
A. The CLASS trial was like other NSAIDs. I can offer the same data.
Q. I know we're getting conversational here, but let me finish my question, please.
A. All right.
Q. Prior to the start of the CLASS trial -- withdrawn.
You're not familiar enough with the Diclofenac data to offer an opinion about what had been shown pre-CLASS; is that fair?
A. With Diclofenac.
Q. Okay. Is that fair to say?
A. Diclofenac versus --
Q. -- Celecoxib?
A. -- Celecoxib.
Q. You can't offer an opinion on that?
A. I can't offer an opinion.
Q. All right. And as it relates to ibuprofen, you believe that before the start of the CLASS trial it had been proven that ibuprofen produced more endoscopic ulcers and more symptoms than Celecoxib, correct?
A. At those doses.

Q. And, so, any of the data that came out of the CLASS comparing Celecoxib to ibuprofen on the measure of endoscopic ulcers and symptoms, you would agree with me, according to the dichotomy that you presented to us before, might be hypothesis generating but just further data on something that had already been proven. Is that fair?
A. It would be a way to potentially game the study if that was one of your outcome measurements.
Q. You keep saying "game" and I'm actually trying to be neutral and you keep trying to inject motivation and I'm going to ask you about that in a second. But I'm going to have the court reporter read back my question and I'm wondering whether you can just answer the question that I've asked.
MR. SAHAM: And I would object, asked and answered. He just answered it.
(Question read back for the record.)
MR. SAHAM: And I would read back his answer as well, please.
(Answer read back for the record.)
MR. DOUGHERTY: So you need to read back my question again so that the witness can focus on my question.
MR. SAHAM: She just read your question and

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his answer.
MR. DOUGHERTY: Scott, just let me take my deposition here.
(Question read back for the record.)
Q. (BY MR. DOUGHERTY) You can answer the question.
MR. SAHAM: Objection, asked and answered. The record reflects an answer to that question.
Q. (BY MR. DOUGHERTY) Go ahead, Dr. Graham. You can answer.
A. You would not know on an individual trial how -- you know, for the outcome. But the fact that those doses it was known, proven, if you like, that Celecoxib was less likely to cause dyspepsia, one problem, and endoscopic ulcers than the high doses of ibuprofen that were being used.
Q. And that had been proven even before CLASS was finished?
A. Even before CLASS was started.
Q. Okay. All right. And some of the data that comes out of CLASS relates exactly to that question, you agree?
A. Indirectly.
Q. And nothing in CLASS disproves what had already been proven on the dyspepsia and endoscopic ulcers compared to ibuprofen, correct?

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A. Well, CLASS didn't really set out to look for endoscopic ulcers or -- but it did set out to look for symptoms; because the endoscopic ulcers implies that you endoscope at a regular interval.
Q. Right. So the answer to my question is that nothing in CLASS disproved what had already been proven as it relates to ibuprofen, correct?
MR. SAHAM: Objection, form, foundation.
A. It didn't test the hypothesis, so it couldn't disprove.
Q. (BY MR. DOUGHERTY) The -- you've raised an important distinction and I think we ought to just explore to make sure we have a common understanding.
All of the endoscopy trials that you were involved in involving COX-2's required per the protocol for the investigators to scope at regular intervals, correct.
A. Correct.
Q. There wasn't a clinical judgment being made about whether or not to scope a patient, correct?
A. It was, generally, also a clinical judgment about whether to scope; and you scoped at intervals and then you could scope at other intervals.
Q. In between, okay, right. But you understand that in the CLASS trial there was no periodic scoping

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requirement, correct?
A. Right.
Q. The investigators, including maybe some of the people that worked for you, scoped only when they made a clinical judgment to scope, correct?
A. Correct.
Q. Okay. And when they scoped, they did not know whether they were scoping a patient that was on Diclofenac, ibuprofen or Celecoxib, correct?
A. Not quite -- not absolutely correct about that, but not quite about the other, about why they decided to scope. They were encouraged to scope. So it's different in a trial than it is in a clinical practice.
So in a trial you have a protocol that says you talk to the patient and if there's any question you go do this. So they're encouraging you to do that.
Now, in the Rofecoxib one, they really encourage you to do that. This one was much more open, but you were encouraged to ask. You were encouraged to look. I like to say they weren't as smart as the Vioxx people, but that's -- you know, they didn't go all out to game it; but they couldn't help it but get some false positive results.
Q. What in the CLASS protocol, Dr. Graham, do you believe constitutes the encouragement to scope?

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A. We can go read through the protocol.
Q. You used --
A. It talks about when you see the patient, you know, you ask them, et cetera, in that it gives kind of the judgment that, you know, when you're in any doubt, you should take a look. And it's not pushed hard like the other one and they didn't push hard.
Q. They didn't push hard?
A. (Witness nods head.)
Q. Well, what set of symptoms were the investigators asked to consider making an independent judgment about whether or not to scope? What were the factors?
A. It -- I mean, it's difficult to explain the different way that you manage a patient in a clinical trial versus real practice. The threshold is clearly different depending on kind of what the -- what expectations of someone else is.
Q. And I'm just asking you to --
A. I can --
Q. Let me put it to you this way.
A. I can find those for you.
Q. Hang on a second.
Do you intend to offer an opinion in this case that the site investigators of the CLASS trial were encouraged to scope patients? Are you going to offer

that opinion in this case?
A. I wasn't planning on it.
Q. Okay. And right -- you have no way to point to anything right now in the protocol that would support any position that they were encouraged to scope, correct?
MR. SAHAM: Objection, form, foundation. You won't put the protocol in front of him, John, and he says he has no basis, I mean.
A. I'm confident I could find it in the protocol.
Q. (BY MR. DOUGHERTY) But you don't intend to offer any opinions in this case that the investigators in CLASS were encouraged to scope, correct?
A. Not unless you ask me the question.
Q. Well, it doesn't really work that way, Dr. Graham. The question is: Do you intend to testify in this trial --
A. No.
Q. -- that the CLASS investigators were encouraged to scope?
A. No.
Q. Dr. Graham, do you believe -- and I think I know the answer to this, but I'll ask it to you, anyways: Is it your opinion that endoscopic ulcers are not biomarkers for complicated ulcers?

A. Endoscopic ulcers do not have clinical significance for prediction of clinical ulcers, right.
Q. If you confirm that a patient has an endoscopic ulcer in your practice, Doctor, isn't it fair to say that one of the things that you are worried about is whether or not that patient is going to develop a life-threatening complicated ulcer?
A. No.
Q. So, do you want every patient that comes to you and do you want all of your colleagues in the medical community to believe that it's your position that when a patient presents to them and they confirm through endoscopy that that patient has an ulcer that that doctor should not worry about that patient developing a complicated ulcer?
MR. SAHAM: Objection, form, incomplete hypothetical --
Q. (BY MR. DOUGHERTY) Go ahead.
MR. SAHAM: -- assumes facts not in evidence.
A. What we teach is that when you endoscope a patient and you see these little mucosal abnormalities because they're taking aspirin or something else, that you ignore them.
Q. (BY MR. DOUGHERTY) But you're not treating that

patient based upon the confirmation that they have an ulcer, you're not treating them as if they could develop a complicated ulcer?
MR. SAHAM: Objection to form.
A. Remember, an ulcer frequently what was called an endoscopic ulcer is for study only; and they would never be called an "ulcer" clinically. You would call it an erosion and you would say "You're taking aspirin, aren't you?"
"Yes, I am."
"Thank you very much, no problem."
If I take 100 people and I give them two aspirins or three aspirins and I scope them, essentially, 100 percent will have mucosal abnormalities when I scope them the next morning.
Q. (BY MR. DOUGHERTY) So your advice to all the medical -- all medical professionals is: You should ignore -- let me put it this way: Your advice to all medical professionals is "Even if you confirm that your patient has an endoscopic ulcer, an ulcer viewed in the endoscope, that they should not treat that patient as if they are at a higher risk for complicated ulcer." Is that your position?
A. That is not the definition of an endoscopic ulcer.

MR. SAHAM: Objection, form, foundation, in completed hypothetical.
MR. DOUGHERTY: All right. Let's take a break.
THE VIDEOGRAPHER: We're now going off the record. The time is, approximately, 12:05.
(Whereupon, a lunch recess was taken from 12:05 p.m. to 12:54 p.m.)
THE VIDEOGRAPHER: We're now back on the record with tape No. 3 with the deposition of Dr. David Graham. The time is, approximately, 12:54.
Q. (BY MR. DOUGHERTY) Dr. Graham, it's your opinion that -- is it your opinion that symptomatic ulcers are not predictive of complicated ulcers?
A. Symptomatic endoscopic ulcers or symptomatic -- what kind of ulcers?
Q. If you want to make a distinction for the purposes of the answer between symptomatic ulcers and endoscopic ulcers, that's fine.
A. Yes, there's no prediction.
Q. And is that based upon your review of clinical trial study data?
A. It's based upon, in part, my own research.
Q. And, just briefly, summarize what that research shows.

A. Well, we did two trials that -- where we looked at endoscope patients who were chronic NSAID users and we compared the frequency of symptoms and the frequency of ulcers and we found that symptoms were common, ulcers were uncommon, and most of the ulcers were in asymptomatic people.
Q. Were you looking specifically at endoscopic ulcers there?
A. No, we were looking at clinical ulcers -- real ulcers.
Q. Are those the trials that you mentioned in your report, Dr. Graham?
A. Right, same ones Dr. Wang mentioned.
Q. Could you pick up your report, Doctor?
A. I have it right here.
Q. I want to go to where you mentioned those trials in your report and make sure we're on the same page. Can you turn to the discussion that begins on Page 21?
A. Okay.
Q. And if you take a look at Paragraph 32. And let me just ask you this as a preface to getting into the discussion. You write in Paragraph 32, quote: "It was known at the time of the CLASS study that NSAID use is one of the most common causes of drug-induced dyspepsia, such that any trial of patients receiving NSAIDs is

expected to have a considerable number with what Dr. Wang calls the dyspeptic syndrome." Do you see that?
A. Yes.
Q. And is that your opinion? Do you stand by that?
A. Yes.
Q. So that by the time the CLASS trial had started, it was known that NSAID use is one of the most common causes of drug-induced dyspepsia?
A. Yes.
Q. And you think that's been proven or was proven even before CLASS started?
A. Oh, it's probably been known since the early '60's.
Q. Okay. And I'm making a distinction in my question, Doctor, between "known" and "proven," using the dichotomy that you had kind of laid out for us before. Do you think that it had been proven prior to the time of the CLASS study that NSAID use is one of the most common causes of drug-induced dyspepsia?
A. Yes.
Q. Okay. And is it common, Doctor, that dyspepsia is not predictive of either symptomatic or endoscopic ulcers?
A. Yes.

Q. And do you believe that that opinion is widely shared among gastroenterologists?
A. Yes. And, actually, it's -- it was part of the study design. On Page 24, I quote from the study design where they say exactly the same thing; and the FDA says it in their book, also. I mean, everyone says it.
Q. Can you just tell me where you're pointing to, Doctor, so that we can -- so that I can be sure?
A. Page 24.
Q. Yes.
A. You see the quote?
Q. Yes.
A. That is a quote from the Searle/Pfizer.
Q. Just so the record is clear, are you talking about the block, quote, that you put on Page 24 of your report that begins --
A. That is right.
Q. -- with "Burning epigastric pain"?
A. Right.
Q. And you highlighted and italicized that sentence in the middle of that quote?
A. Well, they may have, too. I don't know if I did that separately, but okay. But, yes, that's the one.
Q. And this statement says "It is important to note" -- I'm quoting now -- "It is important to note

that there is a lack of concordance between symptoms and GI ulcers or serious events i.e., many patients who exhibit symptoms do not have ulcers, while many who have endoscopic ulcers do not have symptoms." Is that what you're referring to?
A. That's right.
Q. And can I complete the actual quote there? Because it goes on to say -- which you didn't bold and highlight -- "Despite this fact, these symptoms are sufficiently distressing in that at least 10 percent of patients receiving NSAIDs to cause discontinuation of drug use, thereby losing the benefit of continued treatment."
Do you see that?
A. Right.
Q. And do you agree with that statement, sir?
A. Yes.
Q. Okay. Do you believe that it is -- that it is commonly accepted among gastroenterologists in the United States that dyspepsia is not predictive of an ulcer or do you think that question's still being debated?
A. The most common of dyspepsia in the United States is called the "non-ulcer" dyspepsia.
Q. I know. I'd like you to answer my question,

though.
A. It's called "non-ulcer" dyspepsia because they have dyspepsia and no ulcers.
Q. You're still not answering my question. Should we ask -- should we have it read --
A. Yes -- the answer to your question is: Yes, most gastroenterologists believe that dyspepsia is not a common -- ulcers -- that dyspepsia is not a predictor -- a common predictor of an ulcer.
Q. I want to make sure that I --
A. People with ulcers, not NSAID ulcers, but people with real ulcers commonly have dyspepsia. Most people with dyspepsia do not have ulcers.
Q. Right. But isn't it fair to say, Dr. Graham, that people with dyspepsia are at a higher risk of developing an ulcer than people who don't have dyspepsia?
A. In our study in patients that had -- NSAID users with ulcers, more ulcers were in patients without dyspepsia and more non-ulcers were in patients with dyspepsia.
Q. So, let me go back to my question -- and I appreciate that -- and we're going to get to those two studies that you reference.
Is it your opinion that people with

dyspepsia are not at a higher risk of developing an ulcer than people without dyspepsia?
A. Yes.
Q. And would you -- and that's based upon your review of the clinical trial data and your own studies?
A. That's just clinical medicine.
Q. If a -- so, just to be clear, if a patient prevents to you with dyspepsia --
A. An NSAID user?
Q. -- an NSAID user in a clinical setting, not in a clinical trial setting, but in a real world clinical setting, if a patient prevents to you with dyspepsia, are you going to tell that patient that they are not at a higher risk of developing an ulcer?
A. I'm not going to bring up their risk. I mean, they either have an ulcer or they don't have an ulcer. "Risk" is a different question entirely. "Risk" is a predictive thing.
Q. Let me try it another way: Are you going to treat a patient with dyspepsia as if they could develop an ulcer?
A. Dyspepsia ulcer correlation is people with ulcers often have dyspepsia. Dyspepsia is one of the symptoms of an ulcer. So it's not predictive that "I will develop an ulcer." It is predictive of "You have an

ulcer."
Q. So dyspepsia is predictive of an ulcer?
A. It is one of the symptoms of an ulcer, but dyspepsia is very common.
Q. So people with dyspepsia because it's a symptom of an ulcer may, in fact, have an ulcer at a higher rate than people that don't have dyspepsia?
MR. SAHAM: Objection, misstates prior testimony.
A. That's not what I said. And, more importantly, NSAID users often have ulcers with no dyspepsia. They have ulcer complications with no dyspepsia. That is explained and not understood, but it's explained because they're taking a pain medicine. So they have the ulcer and no pain and, yet, they have a complication.
So one of the clinical dictums is lack of symptoms does not help you in the patient taking NSAIDs that has an ulcer complication.
Q. (BY MR. DOUGHERTY) Let's just agree that an asymptomatic patient can develop an ulcer. Let's just agree with that, okay, for purposes of this question.
A. And they're more likely to be NSAID users.
Q. Now, my question is: Is an NSAID user who has dyspepsia more likely to have an ulcer than an NSAID user without dyspepsia?

MR. SAHAM: Objection, asked and answered.
A. And the data are that -- if there's either no data on the question or the data would say "no."
Q. (BY MR. DOUGHERTY) So, now let's explore what the basis for that opinion is; because you're taking the position that, "no," a dyspeptic NSAID user is not at a higher risk of having an ulcer. What data supports that opinion?
A. It was -- we were reading it on Page 21. You were about to read it to me.
Q. Okay. On Page 21 and 22 you talk about two trials that you've conducted, correct?
A. Correct.
Q. I'm asking about other data that supports your opinion?
MR. SAHAM: In addition to what's on 21 and 22?
Q. (BY MR. DOUGHERTY) Yeah, we're going to talk about the two studies that you reference here.
A. If you go to the literature, these are the studies they recom- -- that they quote. These are the studies that your consultant quoted.
Q. I'm going to ask again: Other than these two studies, Doctor, what data would you point to support your opinion that dyspeptic NSAID users are not at a

higher risk of having an ulcer than non-dyspeptic users?
A. I would -- I mean, it's one of those things that may be wrong, but everyone knows; and the FDA even puts into their package inserts.
Q. Well, the package insert doesn't mention dyspepsia.
A. And these --
Q. You can see that.
A. -- these are two studies that I know about that most people quote, so....
Q. Okay. You're unaware of any other data?
A. There may be others, but these are the ones I know.
Q. Are you aware of data that contradicts your opinion?
A. From -- am I aware of studies that have data that contradict my opinion?
Q. Correct.
A. No. I mean, I know that from the -- from the CLASS study they found some correlation, but that's -- remember, that's data from within the study, not from an outside study. It wasn't a prospective, a study, a study, a study. It was -- it came out of the study, so you have to throw it out.
Q. Well, you're not suggesting they throw it out.

It might be of interest, right?
A. It might be, but it doesn't fit with what's known so you tend to throw it out.
Q. And you can see that, I think, in your earlier answer that your opinion about dyspeptic NSAID users that that could be wrong, correct?
MR. SAHAM: Objection to form.
A. I hope not.
Q. (BY MR. DOUGHERTY) It could be, right?
A. Anything could be.
Q. Well, you only cite the two studies, Doctor, and are aware of no studies contradicting?
A. These are two studies to answer -- to address -- prospectively done to address that question.
Q. So, let's look at these two studies.
A. All right.
Q. And I reference one of them, I think, had 65 patients in it?
A. Right.
Q. And the other one had 245 patients in it?
A. Right.
Q. So, let's talk about the 65 patients. What percentage of the patients in that trial who were dyspeptic NSAID users developed ulcers?
A. We don't know anything about developing. This

was a cross-sectional study.
Q. So, let me ask the question in a slightly different way, maybe, to get to where you want to be.
How many of the 65 patients in the trial that you reference here on Pages 21 and 22 of your report were NSAID users with dyspepsia who were confirmed to have an ulcer?
A. Well, I'd point out that only 32 percent -- one-third of the patients had normal stomachs. And it says "dyspeptic symptoms are present in 19 percent of those with complete normal endoscopy, but only 9 percent of those with abnormal endoscopic findings."
Q. Why don't we mark the -- you published the results of that study, did you not?
A. Oh, yeah.
MR. DOUGHERTY: Let's make this as 1055.
(Exhibit No. 1055 marked.)
MR. DOUGHERTY: Here you go, Scott.
MR. SAHAM: Thank you very much.
Q. (BY MR. DOUGHERTY) Doctor, you have in front of you Exhibit 1055. Is that the publication that contains the results of the study referenced on Page 21 and 22 of your report?
A. Yes.
Q. And, in fact, if you look at footnote 21 of your

report, just confirm that the article cited is the same that you have in your hand at 1055 the article referenced in footnote 21?
A. Same.
Q. Do you believe that a clinical trial involving 65 patients was sufficiently powered to answer the question of whether or not dyspeptic NSAID users were at greater risk of having an ulcer than non-dyspeptic NSAID users?
A. You get the answer to that question by more than one study.
Q. Well, why don't we just focus on the question that I asked. Was this study sufficiently powered to answer that question?
A. This study was not sufficiently powered to answer that question.
Q. And, in fact, that question was not the primary endpoint of this study, correct?
A. That question was not the primary endpoint of this study.
Q. So, the conclusions that you reach on the basis of this study are, to use your dichotomy, simply hypothesis generating, correct?
A. Well, I would refer you to Page 1155 and the discussion in the middle of the first paragraph. It

said "Overall 12.3 percent of our patients had dyspeptic symptoms, which is similar to the 15.9 percent recorded by Gibberd among 515 rheumatoid arthritis patients attending a Rheumatology Clinic." Is 515 a better number?

Q. Are you finished with your answer, sir?

A. Yes.

MR. DOUGHERTY: Madam Reporter, would you please read back my question to the witness?

(Question read back for the record.)

MR. SAHAM: Objection, asked and answered. I believe the transcript will represent a multi-line answer to that very question that was read by the court reporter.

Q. (BY MR. DOUGHERTY) You're required to answer my question, Doctor.

A. My answer is that in this paper in the discussion there are a review of the other literature related this, including patients with 500 patients and other patients with 300 subjects, all coming up with the same answers, which would seem to me that that would be reasonable confirmation of the findings in the study.

Q. Let me try it another way, Doctor: Do you believe that this study proved that dyspeptic NSAID users were not at a greater risk of having an ulcer than

non-dyspeptic NSAID users? Did it prove that?

A. It showed this and the other studies that the presence of symptoms was not predictive of the presence of an ulcer.

Q. I'm not asking about other studies. We'll get to that in a minute. I'm asking about this clinical trial that you've conducted. Did it prove that dyspeptic NSAID users were not at greater risks for ulcers than non-dyspeptic NSAID users?

MR. SAHAM: Objection, form, asked and answered.

A. There are no non-NSAID users here.

Q. (BY MR. DOUGHERTY) So, the answer to my question it didn't prove that point at all?

MR. SAHAM: Objection, form, foundation.

A. I don't understand. You'd have to define to me what proof would be --

Q. (BY MR. DOUGHERTY) Well, you know --

A. -- or come as close you can get.

Q. I find it interesting, Doctor, and I just want to give you the opportunity to explain to the jury why you're now implying a double standard; because your report is critical of the JAMA publication of the CLASS trial on the basis that it didn't prove what the author said it proved. You said "at most it's hypothesis

generating" because the data presented in the JAMA included things that were not in the primary endpoint. And, yet, when we apply that criticism to your own paper, sir, you are reluctant to apply the same standard equally to what the results of your own than clinical trial were?

MR. SAHAM: Objection, form, foundation, assumes facts not in evidence, incomplete hypothetical.

Q. (BY MR. DOUGHERTY) So, go ahead.

A. I see what the problem is, is that it's you misunderstand the papers. One was a clinical trial, you know, with a comparative group. This is a cross-sectional descriptive study that describes a -- an event. That's all. And it relates to the other cross-sectional descriptive studies.

And a cross-sectional descriptive study, if you like, can never prove anything. What it does is describe. It describes that most people in America with skirts are women. That doesn't prove that everyone in a skirt is a woman.

So these data, when you look and you say then "How does it relate to the previously published data" and you find it's completely consistent. Now, for a cross-sectional study you can never get proof; but it's as close as you can come.

Q. So what data do you rely on, other than this study and the other study that we're going to look at in a second, to support your opinion that dyspeptic NSAID users are not at greater risk of having an ulcer than non-dyspeptic NSAID users?

MR. SAHAM: Objection, asked and answered.

A. I would think that my relying on the moment is not only on studies, but this is conventional wisdom that is in every textbook and every review et cetera, et cetera, so that I only know of one exception -- and it's not even a good exception -- because in that study that you're discussing the patient didn't necessarily have to have symptoms to have a symptomatic ulcer.

Q. (BY MR. DOUGHERTY) Okay. Let's take a look at your study results that were published here in 1055. You referenced a Table 4, Dr. Graham, of the patients -- of the 65 patients in this trial who presented with symptoms. How many of them as a percentage, when scoped, were determined to have an ulcer?

A. Well, it was 10 out of 65. So it's about, what, 19 percent, I think, is what we said.

Q. 19 percent shows a normal endoscopy, though, Doctor.

A. Oh, whatever it is. It's 10 out of 65, one out of six. That's about 17 percent.

Q. Doesn't your Table 4 show that of those with symptoms present --
A. Oh, no, ulcers. There were 10 ulcers, most had no symptoms.
Q. Doctor, let's keep focused back on my question.
A. Okay. I'm sorry.
Q. Just tell the jury in this study of the patients with symptoms present, what percentage of them were confirmed to have an ulcer by endoscopy? It's right there in Table 4, Doctor.
A. I'm after the count. It's seven out of eleven -- I mean three out of eleven.
Q. Well, actually, what you say in your article -- and I don't know why you're reluctant to just say it -- is that 30 percent of those presenting with symptoms were confirmed by endoscopy to have an ulcer. Am I misreading that table, sir?
A. That's what I said. It's three out of -- whatever that is -- numbers -- three out of eleven, 30 percent.
Q. We don't have to guess because you actually concluded the percentage. Just tell the jury what the percentage is.
A. 30 percent.
Q. That wasn't hard.

MR. SAHAM: Objection, argumentative.
Q. (BY MR. DOUGHERTY) So, 30 percent of those with symptoms were confirmed to have an ulcer. That's what your own research shows, correct?
A. Right. And 70 percent of those with ulcers did not have symptoms -- or percentages.
Q. So, since your own study shows that 30 percent of the patients in this trial who presented with symptoms, in fact, had ulcers, do you stand by your opinion that ulcers -- that patients on an NSAID with dyspepsia are not more likely to have peptic ulcer disease --
MR. SAHAM: Objection, misstates prior testimony and form.
Q. (BY MR. DOUGHERTY) -- than patients on NSAIDs without dyspepsia?
MR. SAHAM: Same objection.
A. Which is what the data shows, 70 percent versus 30 percent
Q. (BY MR. DOUGHERTY) Doctor, is it your opinion, in light of your own research here, that patients on an NSAID with dyspepsia are not more likely to have peptic ulcer disease than patients on NSAIDs without dyspepsia?
A. Yes.
Q. A work-up for dyspepsia -- do you work up patients with dyspepsia?

A. Of course.
Q. Doesn't that work-up include looking for peptic ulcers among the more likely causes?
A. There's arguments about that.
Q. Let's ask -- let me ask about your practice because I was --
A. My practice would be -- remember, when you come to a gastroenterologist, you get scoped.
Q. So, you're actually not in a position -- because you scope when they arrive -- you're not in position to offer an opinion?
A. No. I mean, I'm just saying if you go to the family doctor, it will be a different question. They list -- here's an algorithm for working up dyspepsia and it doesn't list endoscopy is the first thing to do. It lists the clinical trials the first thing to give them, some PPIs and see what happens.
Q. Isn't every medical student in the United States been taught for the last 30 years that if a patient presents with dyspepsia, they are at risk of having an ulcer --
MR. SAHAM: Objection, form, foundation.
Q. (BY MR. DOUGHERTY) -- and that the ulcer is more likely -- is among more likely causes of that dyspepsia?
MR. SAHAM: Same objection.

A. They are taught that most patients that present with dyspepsia have nothing that you will find. Of the causes of the patients with ulcers and with dyspepsia, peptic ulcer disease is definitely one of the more common causes.
Q. (BY MR. DOUGHERTY) Right.
A. It may be an exception with an NSAID user.
Q. What basis do you have to believe that there's an exception to that rule for NSAID users, Dr. Graham?
A. Well, one of the questions that comes above, what you do is "are they taking NSAIDs, are they taking symptomatic drugs that are commonly associated with symptoms"; and, then, you say that's likely to be drug-induced and not necessarily due to a structural abnormality.
Q. Ulcers -- dyspepsia is a symptom of an ulcer, is it not?
A. It's a symptom of which one of the causes is an ulcer.
Q. And one of the causes of that could be the taking of NSAIDs, correct?
A. Could be.
Q. Is there a difference in dyspepsia rates between traditional NSAIDs and COX-2's in your opinion?
A. It's dose-related.

Q. So, is there a difference?
A. If I were taking a patient that I was giving him, let's say, one Aleve a day or two Aleves a day, probably not. If I were giving him a full arthritis dose for rheumatoid arthritis, definitely.
Q. I appreciate that, but let's separate the world into COX-2's and traditional NSAIDs for a moment. Can you accept that framework for my question?
MR. SAHAM: Objection, form, foundation.
A. No.
Q. (BY MR. DOUGHERTY) No, I'm asking you to, Doctor. You're the expert. I'm asking you a hypothetical question.
A. Okay. We will make your NSAID Diclofenac.
Q. Is there a difference in the dyspepsia rates between traditional NSAIDs and COX-2's?
MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.
A. Well, if I answer it now being Diclofenac.
Q. (BY MR. DOUGHERTY) Let me try it another way --
A. We can look at the CLASS study and we can ask, "Well, there's a difference in dyspepsia between the Diclofenac and the Celebrex."
Q. Do you know what that data shows?
A. No.

Q. Because you haven't done that?
A. No, I have seen that data. But I don't know what it shows, but I think it shows that they're the same --
Q. Are you aware of any research --
A. -- I think so.
Q. -- are you aware of any research that attempts to answer the question of whether or not there is a difference in the rate of dyspepsia between traditional NSAIDs and COX-2's?
A. That's not a marketing study? A marketing study means the doses are not equivalent that are using the highest dose of one versus an average dose of another. The neat thing about Celecoxib is you don't get more symptoms as you go up on dose.
MR. DOUGHERTY: Can you read back my question, please?
(Question read back for the record.)
MR. SAHAM: Objection, asked and answered.
Q. (BY MR. DOUGHERTY) Please answer my question, Dr. Graham.
A. Yes.
Q. And what is that?
A. It shows a remarkable difference in rates and related to dose, in particular, and the drug.
Q. Just, generally, describe those differences,

please.
A. There are certain NSAIDs, such as Nabumetone, that has rare symptoms. And, so, there are low symptomatic NSAIDs and then there's high symptomatic NSAIDs and there's a dose-related phenomenon. That's, in general, the answer; though I could pick an outcome of a study, if I wanted to do a study, by choosing the doses and the drugs.
Q. Do you believe that it has been proven that the rate of dyspepsia among traditional NSAID users is higher as a CLASS versus the rate of dyspepsia for COX-2 users as a CLASS?
A. I know the marketing studies would suggest that I don't know the answer to that question, because I would have to look at individual studies. I know the marketing people would like to say that, but I'm not sure that it's factual.
Q. You keep talking about marketing studies, and I just want to kind of peel that back a little bit because I detect some cynicism in there.
You are drawing a distinction between trials done for marketing purposes and trials done for other purposes. And I'm assuming that you only do research for the other purposes; is that right?
A. Currently, yeah.

Q. And do you believe that no marketing study, using your definition, can be relied on?
A. No, it has to be looked at with a grain of salt.
Q. Just as your research needs to be looked at with a grain of salt, right?
A. Mine was a cross-sectional study confirming ten other studies.
Q. Not that research, your entire body of research?
A. Oh, I don't think so. I think our studies are -- try and ask what reality is.
Q. Name me one Celebrex marketing study that you believe cannot be relied on?
A. CONDOR.
Q. Why is that, Doctor? I thought you didn't know anything about the CONDOR trial when I asked you earlier about it?
A. Well, you just asked me to name one. I gave you one, "CONDOR."
Q. Why is that?
A. Well, because they -- remember, they didn't ask dose equivalents. They asked high dose, low dose, enteric-coated products, which tend to cause damage downstream in the small bowel, et cetera.
Q. So, you're criticizing the design of that study or you're criticizing the results of that study?

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A. No, I'm just saying it's a marketing study. You decide what the results are and then you set up a study to get you those results. That's a marketing study. You're not asking reality. You're asking "I want these results and I could use them to sell my drugs. So I'll go them. Can I get them?" And if you don't get them, then you don't publish.
Q. Sir, do you believe that the people involved in the CONDOR study, the scientists involved in the CONDOR study that their papers can't be trusted because they're so-called marketing studies, using the Graham framework?
MR. SAHAM: Objection to the form of the question, foundation, incomplete hypothetical.
A. The conclusions are -- I mean, they can be trusted. They found what they found. But are they interpretable and for as "reality," and the answer is "usually not."
Q. (BY MR. DOUGHERTY) Just as a general rule or are you being specific to CONDOR now, Dr. Graham?
A. No, this is "general rule." This is what marketing studies are all about. That's how they -- that Tylenol killed off aspirin, by showing endoscopic studies.
Q. And you don't think that's a good thing?
A. It's not "good" or "bad." This is what marketing

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is all about. My Chevy truck is better than your Ford truck because I found something it could do, but that yours couldn't; and I made a television commercial about it. I mean, that's what marketing is about. But is it really different? And people have learned when you read marketing, you just take it with a grain of salt.
Q. So your friend Francis Chan, do you know him?
A. Very well.
Q. Did you know that he was the lead author on the CONDOR study --
A. Yeah.
Q. -- article?
A. Yeah.
Q. Do you think that he's been duped and that the results of the CONDOR study that he published are somehow unreliable?
A. He knows how reliable they are.
Q. Do you want to take a look at his article?
A. Huh?
Q. Do you want to take a look at his article and point to me some part of this article that's not reliable or valid and can't be trusted?
A. It's not reliable and valid. It's how you set the study up to get the answer you get.
Q. You don't think this answer that he published in

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the CONDOR study in the Lancet you don't think that answer is important clinically?
A. No.
Q. You think the Lancet just published a marketing study because they didn't have anything else to do that day?
A. No, I think they sold 300,000 reprints.
Q. Is there any limit to your cynicism, Dr. Graham?
MR. SAHAM: Objection, form, argumentative.
A. How many reprints did they sell of the CLASS study?
MR. SAHAM: There's already a stipulated fact on that, if you want to tell him.
Q. (BY MR. DOUGHERTY) So, you're not rejecting so-called marketing studies out of hand. You need to look at them a little more carefully to see whether or not they meet your test; is that right?
A. Whether they -- yeah, that's right. Well, they're not my tests, but whether they are clinically relevant.
Q. You conduct post-hoc analyses as part of your practice, do you not, Doctor?
A. You always look at all the data with the idea to help you design the next study better.
Q. And, in fact, many of your publications present

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post-hoc analyses, do they not?
A. They sure do.
Q. And you would agree that in connection with the CLASS trial it was reasonable for the company and the JAMA authors to conduct post-hoc analyses?
A. Absolutely.
Q. You're not criticizing them for doing that, are you?
A. Absolutely not.
Q. Because there could be in those post-hoc analyses some important differences shown between Celebrex and the comparators in the CLASS trial, correct?
A. There could be important differences suggested that you'd want to follow up on.
Q. And you agree that some of that -- that that information should be shared, correct?
A. Well, it depends if you want to share it or not. It depends on the -- but, yes, in general, it's nice to tell people what you find.
Q. And, in fact, those findings could be important to physicians who are prescribing Celebrex or Diclofenac or ibuprofen, correct?
A. It might be.
Q. And you're not testifying in this case that that information was not important to physicians, correct?

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A. I'm not going to testify whether it was or was not.
Q. In a couple of places in your report, Doctor, you reference the idea of multiple comparisons. Do you remember doing that?
A. Yes.
Q. And in one place in your report, you refer the reader of your report to a report by Dr. Jewel?
A. Yes.
Q. Do you remember doing that?
A. Yes.
Q. So I just want to make sure I understand what you're going to do versus Dr. Jewel, because we've already deposed him. Are you offering expert opinions in this case as to whether or not multiple adjustments needed to be done on the CLASS data in the JAMA article or are you leaving that for Dr. Jewel?
A. No, no, I would testify that they needed to be done; but I would not necessarily testify what they specifically would be. I mean, we all know that -- and we're taught as medical a student if you ask 20 questions, the chances are one in five that will be falsely positive. That's just statistics.
And, so, we all learned that when you ask multiple questions because of that, you need to make

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adjustments to statistical significance. That's just motherhood, "apple pie."
And, so, they did multiple comparisons, you know, that they either need to do adjustments or they need to tell me why they don't need to do the adjustments because everyone knows that they should normally need to do adjustments.
Now, what those adjustments are for the individual study, that's when you call the statistician and say "What adjustment should I make here?" And we all would routinely use Bonferroni's or one of those kind of rules that says you double or triple --
Q. Bonferroni's (Italian), is that what you meant to say?
A. Bonferroni's, that Italian name. But if you ask me, you know, for the individual case what is indicated. I don't know. The concept is every medical student knows that.
Q. But you're not bringing any special expertise to the concept, are you?
A. No.
Q. And whether or not multiple adjustments needed to be done on the CLASS data presented in the JAMA article, you're not going to offer any opinions on that issue, are you?

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MR. SAHAM: Objection, misstates prior testimony.
A. I can offer that they -- that they either need to be done or explain why they weren't necessary.
Q. (BY MR. DOUGHERTY) But you wouldn't know how to do it yourself?
MR. SAHAM: Objection to form.
Q. (BY MR. DOUGHERTY) Or put another way: You're not offering any opinions on how that would be done?
A. I would not offer an opinion upon how the technical expertise technique that one would use to do that. But, you know, that the P value that you have is most likely a better estimate than what reality should be.
Q. So, let's get to the opinion that you want to express, that multiple adjustments should have been done in the JAMA article, even if you're not prepared to say what adjustments or how to do them.
Would you concede with me, Dr. Graham, that there are times when you do subgroup analyses where there is no need to correct for multiplicity?
A. There's exceptions to every rule.
Q. Well that's a truism, Doctor. I'm actually asking you an important question that, I think, is a little bit more than a truism.

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Would you agree with me that there are subgroup analyses that do not need to be corrected for multiplicity.
MR. SAHAM: Objection, asked and answered, form.
A. There must be some, yes. I mean, the --
Q. (BY MR. DOUGHERTY) In all the subgroup analyses that you've published, do you want the jury to believe that you and your co-authors corrected for multiplicity in those papers when you were presenting your P values?
MR. SAHAM: Objection, assumes facts not in evidence, form, foundation, incomplete hypothetical.
Q. (BY MR. DOUGHERTY) Go ahead.
A. I don't know if we have or we haven't. We often, when we do subgroup analyses, don't provide them with statistical data to go with them. So it's --
Q. So, you don't even give them the chance --
MR. SAHAM: Are you done with your answer?
Q. (BY MR. DOUGHERTY) -- to do a multiplicity adjustment?
A. That's the answer, frequently.
Q. So, you and your colleagues author papers where you do subgroup analyses where you, yourself, have done no multiplicity adjustment as a result of the subgroup analyses; is that fair?

A. I can't answer that one way or the other, but I would presume that would be -- that there would be examples of that.
Q. In fact, there are many examples, Doctor, in your published work where you're doing subgroup analyses in presenting P values, but not correcting for multiplicity; isn't that true, sir?
A. I don't know one way or the other. I would presume so. I mean, we become more sophisticated as we go along.
Q. Is this another case where you've got two different standards, one you're applying to the CLASS trial and one you're applying to your own work?
MR. SAHAM: Objection, form, argumentative, assumes facts not in evidence, foundation.
Q. (BY MR. DOUGHERTY) Go ahead and --
A. Just show me a recent work that's got a subgroup analysis and it's not corrected of mine.
Q. Why don't you tell me the last time you published a paper where you did a multiplicity adjustment for a subgroup analyses?
A. I don't know right now the last time I did a paper with a significant subgroup analysis.
Q. Do you want to offer opinion testimony in this case, Dr. Graham, in light of your own practice that the

JAMA authors needed to do a multiplicity adjustment on the CLASS data in the JAMA article?
MR. SAHAM: Objection, form.
A. Either they should do it or they should explain why it wasn't necessary.
Q. (BY MR. DOUGHERTY) And are you willing to apply that same standard to your own work, sir?
A. It would -- the first answer to that question would be -- we'll say "no," that my work and their work are entirely separate. If I -- if I'm a bad guy and run around on my wife, it doesn't mean that I would have to condone it in everyone else.
Q. Well, that's what we call a "hypocrite," right, Dr. Graham?
A. We're all hypocrites at one time or another.
Q. You're being paid to be a hypocrite in this case, aren't you?
A. I'm not being paid.
MR. SAHAM: Objection, form, argumentative.
Q. (BY MR. DOUGHERTY) Oh, because you're giving the fee away, you feel like it's okay to be a hypocrite?
MR. SAHAM: Objection, form, foundation --
Q. (BY MR. DOUGHERTY) Is that what you're saying?
MR. SAHAM: -- assumes facts not in evidence.

A. If someone tell us me they've never been a hypocrite, then they, obviously, have some problem with their memory or their mind.
Q. (BY MR. DOUGHERTY) I'm wondering whether you're taking this assignment seriously, Dr. Graham, in light of what you just said.
MR. SAHAM: Objection, argumentative, form.
Q. (BY MR. DOUGHERTY) Do you believe it's a proper role for an expert to just come in and say whatever it is that he or she wants to say without with regard to whether it's consistent with his own behavior?
MR. SAHAM: Objection, form, argumentative, foundation.
A. I'm not sure I understand what you just said. That means that the Supreme Court Judge cannot judge unless he has a perfect life.
Q. (BY MR. DOUGHERTY) "He who is without sin should cast the first stone," are you familiar with that?
A. Yeah.
Q. Do you try to live by that principle?
A. In general.
Q. But not in this case?
MR. SAHAM: Objection, form, argumentative, assumes facts not in evidence.
A. In this case also.

Q. (BY MR. DOUGHERTY) So, you bear your assignment in this case as simply providing you with an opportunity to criticize people for not doing something that you, yourself, have not done --
A. You know --
Q. -- but at the end --
MR. SAHAM: Stop.
Q. (BY MR. DOUGHERTY) -- and at the end of the assignment, you want to take confidential shall information that's produced in this case and write an article about it?
MR. SAHAM: Objection --
Q. (BY MR. DOUGHERTY) Is that not -- do I have your assignment --
MR. SAHAM: Objection, form.
Q. (BY MR. DOUGHERTY) -- your understanding of your assignment correct?
MR. SAHAM: Objection, form. Just give me a chance to object because it's an objectionable question. Objection, form, foundation, assumes facts not in evidence, argumentative, incomplete hypothetical; but you can answer.
A. We have not shown that I have not always done corrections upon my subgroup analyses.
Q. (BY MR. DOUGHERTY) What is the difference

between a primary endpoint, Dr. Graham, and a prespecified endpoint?
A. A primary endpoint is the endpoint for which the study is dependent upon whether it succeeds or fails. Prespecified endpoints are making a list of things that you think might be important that you plan to look at. They are theoretically a little bit more important than other things that you happen to dredge up that you decide to look at.
Q. What -- using that definition, what were the prespecified endpoints in the CLASS trial?
A. We'd have to look at those exactly, but there were some.
Q. Yeah, I know you're the expert. Tell me what they were.
A. You'll have to show me the trial. I don't -- I didn't make a list for this purpose. I can tell you one that was not that is often said to be and that was aspirin use.
Q. You don't think the protocol required the site investigators to record aspirin use?
A. No, it didn't list that as a prespecified endpoint that they were going to analyze. It listed that in the garbage things that they might consider to think about.

Q. Wait a minute. Are you saying that in a gastrointestinal safety trial that it isn't important to understand the role that aspirin is playing in the events that you're studying? Is that what you're saying?
A. No.
Q. You agree that it is important to understand that --
A. I'm saying that it got in the protocol late and it got in the big long list, alcohol, smoking, anything else they happen to think about that day. It wasn't listed as a prespecified endpoint. "We think this is important and we're going to analyze it."
There was a list that says at the end if it, kinda like "In consideration we're going to go on with the rest of this stuff, whether dogs had hair or not." I mean just anything that they thought about they stuck in there.
Q. Anything they thought about. I'm sorry, Dr. Graham, let's just be clear. You're not an expert on the state of mind of any of the people at Searle or Pharmacia, are you? You're not offering opinions in this case about their state of mind, are you?
A. Oh, no. I'm offering opinions about the format that you list prespecified analyses versus where you

just don't prespecify what you're going to do, but you make a list of other things you might look at.
Q. In looking at aspirin use, you would agree, because aspirin is a known toxic agent to the GI system is reasonable, correct?
A. It should have gotten in there earlier, though.
Q. That's not what I asked you, Doctor. You agree with me that looking at the --
A. Oh, absolutely.
Q. -- that it was reasonable for the JAMA authors --
A. Absolutely.
Q. -- to look at aspirin use in the CLASS study results?
A. Absolutely.
Q. And you're not criticizing anybody in this case for looking --
A. Absolutely not.
Q. -- at aspirin use?
A. I wouldn't criticize them for anything they looked at.
Q. Do you believe that the aspirin use data presented in the JAMA article is not reliable?
A. Is not reliable? I mean, I think that's the data that they got. Those are the data that came from the trial.

Q. But is the data on aspirin use as presented in the JAMA article reliable or not reliable?
MR. SAHAM: Objection, form.
A. If you did the study again, would you get the same answer? That would be what I would call "reliable"; otherwise, it's a -- it's data that came from the trial and, therefore, data derived and, therefore, are hypotheses to be tested, not definite conclusions to be believed.
Q. (BY MR. DOUGHERTY) One doesn't need to hypothesize about the toxic effect of aspirin on the GI system, though, correct? That's been proven. Do you agree with me?
A. The hypothesis was from the data that aspirin completely negated the beneficial effect, if there were one, from the coxib, not that it was damaging; but it negated the effect, if there were one.
Q. So, let's just go back to my question: Prior to the CLASS trial, it had already been proven that aspirin had a toxic effect on the GI system, correct?
A. Aspirin is an NSAID.
Q. Correct?
A. Dose-related effect.
Q. Aspirin has a toxic effect on the GI system. That's been established for decades, hasn't it?

A. The 1900's or so.
Q. Right. Okay. And, so, going into the CLASS trial in looking for aspirin use, you're not actually hypothesizing about aspirin's toxic effect. You'd agree with me, correct?
MR. SAHAM: Objection, form, foundation.
A. You're not hypothesizing it whether aspirin is toxic, right.
Q. (BY MR. DOUGHERTY) And the presentation of the aspirin results in the JAMA paper, you would agree with me that those results as presented in JAMA are valid, correct?
MR. SAHAM: Objection --
Q. (BY MR. DOUGHERTY) You're not questioning those data?
MR. SAHAM: Objection, form, foundation.
A. I am not questioning that those are the results of the study.
Q. (BY MR. DOUGHERTY) What you're questioning is the conclusions that you can draw from those results; is that what you're saying?
A. I am questioning that -- yes, whether they would be reproducible. You see, at the outset you would not predict, I don't think, that aspirin had this tremendous effect on the coxib, but not on the NSAID.

Q. Do you believe that that's what the JAMA authors were suggesting?
A. That's what they showed.
Q. Are you believing that that's what they were suggesting in the JAMA article?
A. Those are the data. They didn't suggest anything. The authors did a study and they had a null hypothesis and you would expect them to say "We did a study. We've got this null hypothesis. We didn't get it. Sorry about that. And, so, we did a bunch of subgroup analyses, which is very reasonable; and we got these new hypotheses. And now we're going to repeat the study and test these new hypotheses to see if we get the right answer."
Q. Do you remember how the JAMA authors -- and we can pull out the article -- how they presented the aspirin data in the JAMA article and what they said about it?
MR. SAHAM: Well, why don't you pull out the article?
MR. DOUGHERTY: We can pull it out if Dr. Graham needs it in order to answer the question.
A. For patients not taking aspirin, the annualized incidence rates of GI complications alone and combined with symptomatic ulcers are 0.44 versus 1.27 and 1.4

versus 2.91 for patients taking aspirin. And, then, they continue on and then they published that the difference was somewhere was not -- there was a difference with a coxib than not with among the NSAID users upon the amount of -- the proportion with damage.
Q. (BY MR. DOUGHERTY) You just -- you were reading from the JAMA article, Doctor?
A. Right.
Q. The JAMA article on the CLASS trial?
A. Right, the results.
Q. Do you think it's reasonable to conclude that patients not taking aspirin would have a lower rate of gastrointestinal events than people taking aspirin? Do you think that's reasonable?
A. Not from this article. I mean because when you actually look at the data, you'll find that -- we can go find the actual data since you're interested in it -- that the -- well, I don't see that (witness reading article). Now what was your question? I'm sorry.
MR. DOUGHERTY: Could you read my question back?
(Question read back for the record.)
A. It's feasible. I mean, they didn't predict it beforehand or it wouldn't have let them in there like the other guys didn't. But the -- I mean, it's

certainly what they found when they got the data.
Q. (BY MR. DOUGHERTY) Prior to CLASS, Dr. Graham, how many articles had been published showing aspirin's toxic effect on the GI system?
A. Lots.
Q. How many articles had been published showing the increased incidence of GI toxicity in patients taking both aspirin and NSAIDs compared to those taking NSAIDs, but not aspirin?
A. I can't answer that question. It was -- in general, people felt that low-dose aspirin didn't make much of an effect on NSAID users.
Q. Do you believe that today?
A. Yeah.
Q. Would you allow a patient to take prescription strength ibuprofen for her arthritis and take low-dose aspirin without putting them on a PPI?
A. Yeah.
Q. You would?
A. What's prescription strength?
Q. You tell me.
A. Is that 1,200 milligrams? There's no such thing as prescription strength/non-prescription strength for ibuprofen. Ibuprofen has got maximum anti-inflammatory activity at 400 milligrams, basically.

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Q. 400 milligrams how often?
A. One dose. But if you give it three times a day, that's a big dose.
Q. I'm sorry. I just want to -- I don't want to get distracted with this, but I want to make sure I understood what you just said.
You said that ibuprofen has no effect above 400 milligrams per dose?
A. No, I'm saying that the ibuprofen -- the amount of ibuprofen given here was much more than most people need, unless they have rheumatoid arthritis. And the analgesic effect is 200 or 400 milligrams.
So, really, the -- the patient -- it depends on what the patient has and I'm going to rationally give them the drug to the lowest dose for the shortest duration like you're supposed and is aspirin going to make a real difference on that, am I going to make a relationship between them and -- so I'm going to do a basic risk calculation. I'm going to take their age into it, high risk, low risk, cardiovascular, et cetera, et cetera to making my decisions.
Q. So you, in your own practice, don't prescribe ibuprofen above 400 milligrams?
A. Rarely, if ever --
Q. What's the basis for you having said --

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A. -- but I don't treat rheumatoid arthritis.
Q. Right. What's the basis for your testimony that the dose of Celebrex used was low compared to the dose of ibuprofen and Diclofenac used?
A. No, this was a high dose of Celebrex. These are very high doses. The difference between Celebrex, I said, and the other drugs is that the risk doesn't seem to go up with Celebrex.
Q. The risk of what?
A. The GI risk.
Q. Doesn't seem to go up with the dose of Celebrex; is that what you're saying?
A. With the dose. But with ibuprofen and Naproxen and Diclofenac, it clearly is dose-related.
Q. And prior to CLASS, Dr. Graham, what evidence are you familiar with or that you would cite to support your opinion that it is known that Celebrex's affect on the GI system does not increase with dose?
A. Well, you'd go back to the other trials that were done with endoscopic ulcers that found that it didn't seem to make a difference when you went up on dose.
Q. That what didn't seem to make any difference?
A. They didn't seem to get more endoscopic ulcers.
Q. Any other evidence, other than the endoscopy trials?

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A. That's the only other ones I know.
MR. DOUGHERTY: Let's take a five-minute break. I'm going to stay in place if you guys want to walk around.
MR. SAHAM: Sure, sure.
THE VIDEOGRAPHER: We're now going off the record. The time is 1:56.
(Whereupon, a recess was taken from 1:56 p.m. to 2:05 p.m.)
THE VIDEOGRAPHER: We're now back on the record with tape No. 4 of the deposition of David Graham. The time is, approximately, 2:05.
Q. (BY MR. DOUGHERTY) Dr. Graham, in your report you make -- you draw a distinction between symptomatic ulcers and endoscopic ulcers, correct?
A. Probably.
Q. And we talked earlier about endoscopic ulcers in the context of ulcer -- or of endoscope -- endoscopies, excuse me, being done even when the patient is asymptomatic, for example, in the clinical trials that you were involved in for the early Celebrex studies?
A. Right.
Q. And one of your opinions in this case and expressed elsewhere is that that endoscopic data, because it's asymptomatic or can be asymptomatic, is not

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a reliable predictor of complicated ulcers, correct?
A. Not -- no, not really.
Q. "No, not really," that's not your opinion?
A. That's a misstatement.
Q. Okay.
A. Endoscopic ulcers are more complicated. Endoscopic ulcers are kind of a made-up concept and in many instances they are lesions, which if seen at routine endoscopy with a normal person, would never be called an "ulcer."
Q. Are you talking about this in the nature of endoscopy trials?
A. Endoscopy trials or in a patient, yeah, undergoing an endoscopy that's taking NSAIDs, you know, acutely and he has a -- and then they say -- or if you come in to see me and you have symptoms and I scope you and I see a big ulcer, that I say "that's a clinical ulcer." And, then, I ask, "Is it due to NSAIDs, is it due to HP?" I know it's liable get complicated, 25 percent over the lifetime, et cetera, et cetera.
That's entirely different than what an endoscopic ulcer is defined by a trial. Those are made-up definitions; and most of those are acute, most of those are small, most of those are not actually ulcers.

They're called "ulcers," but they're not really ulcers. So, they're endoscopic mucosal damage that meets some arbitrary definition that got smaller and smaller over time and less and less meaningful over time. And, as I pointed, out when we took new data that they used to make those decisions and showed it to the people in Hong Kong; and they said in many instances they would not agree that they were actually ulcers. And, so, that's an endoscopic ulcer.

It's -- as I used to say -- as I said, when I coded those in trials, I would code it "ulcer for study purposes only," which meant if I'd have seen it clinically, I wouldn't have called it an "ulcer." And, so, you're dealing with a concept of something with no clinical -- known clinical significance and then you can add symptoms on top of that.

Q. The people in Hong Kong, what were you referring to there?

A. Your friend Chan, I took a tape -- a videotape --

Q. Oh, what you said -- you told me that earlier.

A. -- and sent it that were used in the Merck studies to define endoscopic ulcers to train the doctors. You remember the doctors that do this are not often trained in ulcers. And the companies, by definition, every time I see an ulcer, I can photograph

it and I can video it. They don't do this. They don't want to go back and look at those again. And, in fact, when they did the studies, they find there's a very high false positive rate for things that aren't there probably. So it's a -- at best, it's a very soft endpoint.

So when you say "ulcer," you have a meaning- -- you think about something deep and meaningful and, I'm thinking about something superficial and meaningless frequently. There's an atlas that I even have published about this. And so, therefore, a clinical ulcer, that's the nice thing about bleeding, perforation, obstruction, those are clinical disease, no "ifs, ands, or buts" about them. All the rest of them are figments of people's imagination frequently.

Q. But, Doctor, if you're measuring GI safety and you want to use an primary endpoint other than perforations, bleeding, and obstructions, what would you use?

A. Why would you want to use any other ones besides the clinically relevant one? The only reason that you'd want to use it is because you -- it's difficult and they are not manipulable. They are real. The others you can all manipulate and try and get the answer you want. And so -- and you can do them quickly and cheaply.

Q. You're not -- so, let's just make sure we're clear here. Are you accusing site investigators or the designers of the CLASS trial of manipulating the ulcer data?

MR. SAHAM: Objection, form.

Q. (BY MR. DOUGHERTY) Are you offering that opinion in this case?

A. Say again.

Q. Are you offering an opinion in this case that the ulcer data from the CLASS trial was manipulated by the designers of the trial or the site investigators?

A. I didn't say that at all.

Q. You're not testifying --

A. And I didn't say that at all. I said that endoscopic ulcers were a soft endpoint. They're not a hard endpoint and that they are one that you can manipulate.

And so, therefore, that's why I stand with the FDA saying "Let's use what happens to real people." The risk of NSAIDs is not little endoscopic ditzels. It's bleeding, perforation, obstructions. So if you want to say we're safer than traditional NSAIDs, prove it with the things that count that are not manipulable and that are clinically real.

Q. Again, are you going to testify in this case that

the ulcer data from the CLASS trial, any of it, was manipulated?

MR. SAHAM: Objection, asked and answered.

A. Any of it in the CLASS trial or the previous trials done before that?

Q. (BY MR. DOUGHERTY) The CLASS trial, sir.

A. I think that the symptomatic ulcer data in the CLASS trial is irrelevant and it was not one of the endpoints of the study and the study was a straightforward study. It was three endpoints. It was one year and they did it and they got "no" for the answer and then they cut the data at 6 months and they didn't tell me the real data and they hid it. And, so, if you say if what's in that study represent what they did, "no."

MR. DOUGHERTY: Can you just read my question back, because I think the witness forgot it?

(Question read back for the record.)

MR. SAHAM: Objection, asked and answered; and as the transcript indicates, there's a multiple line answer to that very question that was just reread.

Q. (BY MR. DOUGHERTY) Answer the question, Dr. Graham.

MR. SAHAM: Objection, asked and answered, argumentative.

A. We'd have to define "manipulated," because the data -- the ulcer data in this study of symptomatic ulcers is not part of the trial.
Q. Do you want me to have her read back the question again, or do you remember what I asked you?
MR. SAHAM: Is that a question that you want him to answer?
MR. DOUGHERTY: Yes.
A. I understood the question you asked.
Q. (BY MR. DOUGHERTY) Are you testifying in this case that the ulcer data from the CLASS trial was manipulated, "yes" or "no"?
A. I don't understand the question. I don't understand the use of the word "manipulated."
Q. It's the word that you've been using, Dr. Graham. That's the definition I want you to apply.
A. Do I say that that they manipulated the data for the ulcers? "No."
Q. You see how easy that was?
A. Using my definition.
Q. The ulcer data in the CLASS trial, let's focus on that for a second. In the CLASS trial, were they doing -- were the ulcers observed there endoscopic ulcers or were they symptomatic ulcers that were then confirmed by endoscopy?

A. According to what I read, the protocol, whenever they found an ulcer, it was called a "symptomatic ulcer" whether the patient had symptoms due to the ulcer or not.
Q. What were the rules for the investigators about when to scope?
A. The rules were pretty thin about when to scope. I mean, they were encouraged to scope; but they weren't overencouraged to scope. The ones that counted were the ones that had -- that they really had to scope is when they had a bleed, a major bleed.
Q. In fact, Doctor, wasn't it left to the judgment of the site investigator whether or not to scope dependent upon the symptoms that the patient was complaining about? Isn't that what the rules of the road were for the CLASS trial?
MR. SAHAM: Objection to form.
A. You always scope for some reason. I mean, it didn't have "If you have symptoms for 1 hour and 27 minutes, it's 'yes' and 1 hour and 12 minutes, it's 'no.' I mean, there was no definition of what symptoms led you to endoscope the patient.
Q. (BY MR. DOUGHERTY) Right. So unlike the ulcer data out of the endoscopic ulcer trial, the ulcer data from the CLASS trial is different because they weren't

being scoped asymptomatically. They were only being scoped when symptoms were present, correct?
MR. SAHAM: Objection, form, assumes facts not in evidence, foundation.
A. That's not what I -- when I read the individual cases, that's not the facts.
Q. (BY MR. DOUGHERTY) What's not the facts, Doctor?
A. When I read the individual cases about the ulcers, patients had all kinds of reasons that they got scoped. And, interestingly, there was no predetermined definition of what an ulcer was that you saw. And a number of the things that they saw would meet no one's definition of an ulcer.
Q. Is it your testimony that the protocol for the CLASS trial did not define the criteria for the site investigator on whether to call an ulcer or not call an ulcer?
MR. SAHAM: Objection to form.
A. The -- most studies will define an ulcer. And we've argued for months and years over whether it's got to be more than 5 millimeters, et cetera. And it didn't have to be an ulcer. It could be a large erosion. But that really wasn't -- there was no definition, endoscopic definitions. There were no photographs. There was no atlas. There were just a few words. And

in many of them, when you read what they saw at endoscopy and called an ulcer would not be ulcers.
Q. (BY MR. DOUGHERTY) Who called -- when you say "they called an ulcer," who called?
A. The committee that made a decision.
Q. So, let's get to this: There's -- you agree with me the patients in CLASS did not have to be scoped, correct?
MR. SAHAM: Objection to form.
Q. (BY MR. DOUGHERTY) They did not have to be scoped on some periodic basis, correct?
A. They didn't have to be scoped.
Q. And the decision to scope was left to the clinical judgment of the investigator, correct?
A. Right.
Q. And, then, whatever the investigator saw was -- and reported out in terms of the existence of an ulcer, was ultimately sent to a committee to evaluate, correct?
A. Right.
Q. Do you know who was on that committee?
A. I know who their names are, sure.
Q. All right. Do you have any opinions of those gentlemen?
A. Nice guys.
Q. Good doctors?

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A. Well, they're endoscopists. They know what they're doing.
Q. They do know what they're doing?
A. Yeah.
Q. And they adjudicated all of those findings?
A. Right.
Q. And the data was unblinded --
A. Right.
Q. -- or the data was blinded, correct?
A. Right.
Q. Blinded, correct?
A. Blinded.
Q. So they didn't know whether they were calling an ulcer in a Diclofenac patient or an ibuprofen patient or a Celebrex patient?
A. Absolutely.
Q. They did not know, correct?
A. They did not know.
Q. And what they were studying in the CLASS trial was, in fact, ulcers, was it not?
A. Many times, no.
Q. "Many times, no"?
A. It's not important because it wasn't an out- -- it wasn't an important outcome variable. Remember, the outcome variable was bleeding, perforation, obstruction

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to win the trial. So, these so-called symptomatic ulcers that you want to argue about, if you want to proceed with that, we can do it. And I can -- we can pull the cases and I can show you the ones and you can show it to anybody in the world; and they'll say "This is not an ulcer.
There's one, the lesion is called "minute." In one, it's called "2 millimeters." The definition in the trial minimum was 3 millimeters with apparent depth; and they describe it -- your adjudicators -- as 2 millimeters.
Q. Why did they do that?
A. I have no idea.
Q. Could it be because the whole trial was actually "find ulcers"?
A. It made no difference because they didn't get bleeding -- no, it ws defined "bleeding, perforation, obstruction." You guys or somebody at Searle decided to make ulcers there because they thought they had a bunch of them. But they didn't even get that when they looked in their outcome. And, then, when they went to a year, they lost even that. They got nothing.
So what they took was nothing and tried to -- take their sow's ear and they ended up with a sow's ear. It may have looked like a silk purse

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briefly.
Q. Well, I'm glad we're getting your opinions; and you will not be surprised to find that you might be alone in those opinions. Let's stay with the ulcers, okay?
A. "In quotes."
Q. You can put it in quotes all you want, Dr. Graham. Did you go through and re-adjudicate all the ulcer calls in the CLASS trial?
A. Sure did.
Q. Every single one of them?
A. I went through every one of those cases.
Q. How many ulcers were there in the CLASS trial?
A. I didn't count them.
Q. Why isn't that in your report, Dr. Graham?
A. Huh?
Q. Why isn't that in your report?
A. Why would it be in my report? I mean, they asked me to adjudicate -- I mean to rebut what he did.
Q. Are you offering opinions in this case about the adjudications of ulcers in the CLASS trial --
MR. SAHAM: Objection, calls for a legal conclusion --
Q. (BY MR. DOUGHERTY) -- when that's not in your report?

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MR. SAHAM: -- foundation.
Q. (BY MR. DOUGHERTY) I just want to know.
MR. SAHAM: Same objection.
A. I wasn't planning to bring that up at their trial. If you would like to bring it up, I'd be happy to bring it up and go over them with you.
Q. (BY MR. DOUGHERTY) Your assignment was to rebut Tim Wang and you just told me that you re-adjudicated all of the ulcers calls in the CLASS trial, but didn't include those in your report. Do I have that right so far?
A. I reviewed --
MR. SAHAM: Objection to form.
Q. (BY MR. DOUGHERTY) Do I have that right so far?
A. I reviewed all of the ulcers in the CLASS trial, right. I reviewed --
Q. As part of your assignment in this case, Doctor, or as part of this article you plan on writing?
MR. SAHAM: Objection, form, foundation, argumentative.
A. I did it for just interest.
Q. (BY MR. DOUGHERTY) Did you do that before or after you wrote your report?
A. I did it before I wrote my report. Dr. Wang said that, basically -- that no one, basically -- he said no

one in their right mind would conceive that these ulcers were not clinically important. I mean, that just was beyond any figment of his imagination. So I went to look at what the ulcer looked like and I found it and I didn't agree with that.
Q. But you didn't include that in your report?
A. Well, it didn't seem to be important. I mean, to me, the report that they -- what the answer was is that they had -- the trial was tasked, very straightforward "bleeding, perforation, obstruction." They didn't get it.
So they brought up extraneous things. Aspirin, well, they got that for the 6 months, but they didn't get it at 12 months. Because they cut 6 months because it looked pretty. Come on.
Q. "Come on" what, Dr. Graham?
A. I mean, it's just amazing what they did with these data. You know, you start -- you read it. They fooled me when they read it when I first got it -- I mean when I quoted this thing for fact. You know, you assume that the guys that are doing this are honestly describing what they did to their co-professionals; and that wasn't the case.
Q. I'm sorry. Are you offering opinions in this case -- I need to make sure I understand what you're

saying, Dr. Graham, because you seem to be on a little bit of a roll this afternoon and you're talking about stuff that you never included in your expert report.
So what I'm trying to figure out is whether or not you intend to testify at trial about some of the answers your giving today. And if you are, you need to tell me; and we'll take it from there and talk with Scott about what you're trying to do here today. But if you're not, you just need to tell me you're not, and we can stick to your report, okay?
MR. SAHAM: Objection, form.
Q. (BY MR. DOUGHERTY) So, here's my question -- here's my question. I have a series of questions. Are you intending to testify at trial about the adjudication of the ulcer data in the CLASS trial --
MR. SAHAM: Objection to form.
Q. (BY MR. DOUGHERTY) -- "yes" or "no"?
A. No.
Q. Are you intending to testify at trial that the authors of JAMA article were attempting to mislead anyone, "yes" or "no"?
A. I think that's self-evident.
Q. Answer my question, Dr. Graham. Are you intending to testify at trial that the authors of the JAMA article were intending to mislead anyone, "yes" or

"no"?
A. I will answer that a slightly different way. I will say, in my opinion, that I don't know what their intention was. I'll just say that the article came that out it's very misleading in relationship to what the study design was and the outcome was.
Q. And where do you cover that in your report, Dr. Graham?
A. I mean that's what it seems to me when I talk about fatal flaws, et cetera, et cetera, and --
Q. Now, you just used the word "misleading." Just tell me where in your report you describe -- you used the word "misleading." Tell me where you say that in your report.
A. If you look at almost anyplace -- take 31 --
Q. Paragraph 31, sir?
A. Yeah.
Q. Yes.
A. It talks about what the study was about. In several places, I talk about what the study was about, what the protocol was designed to do and, therefore, you can easily see what you would expect from that if that was the study design. And when you say, "Okay. This is the study design, that these are the outcome variables." You look at the study and you say "Where are those"; and

they're not there.
Q. What's not there, Dr. Graham?
A. The outcome variables you expect to see.
Q. Yeah, just list them for me.
A. Huh?
Q. Go ahead and list them.
A. You expect to see a year's worth of data.
Q. Why?
A. Because that's what the study was.
Q. Who told you that the year's worth of data was valid, Dr. Graham?
A. No, no. In a clinical trial -- you tell me in a clinical trial "This is what we set out to do," okay? And, then, "This is the answers we got." And, then, you say "But, you know, part of this is invalid. For the following reasons, it's invalid." But you don't not tell me that you -- that this was the study we did. You're saying that they had the right to take what they really did and not tell anybody or not tell me what they had done and what answers they got.
Q. You didn't know, Dr. Graham, that the CLASS trial went for 12 months?
A. Huh?
Q. You didn't know that the CLASS trial went for 12 months?

A. I think when this study came out --
Q. Did you know or not know that the CLASS trial went for 12 months?
A. When this study came out, it was a 6-month study.
Q. No, no. That's not my question, sir. Did you not know that the CLASS trial went for 12 months?
A. When the study was published, I did not know that it went for 12 months.
Q. When the results of the trial were announced in April --
A. When the study --.
Q. -- in April of 2000?
A. When this paper came out, when it was presented on the DDW, I did not know that it was not 6 months.
Q. You're saying that paper was presented at DDW?
A. Wherever it was presented.
Q. You didn't --
A. The only time that I became really aware that it wasn't is when the FDA came out and said "Wait a minute, guys. You know, there are more here than meets the eye" and it didn't hold up.
Q. Can you not tell from reading the JAMA article that it went longer than 6 months? Is that your testimony?
A. I'm saying that it's obfuscated or whatever, that

it went longer than 6 months.
Q. No, I didn't ask you whether anything was obfuscated. I'm asking whether or not you can tell from reading the JAMA article that the trial went for longer than 6 months?
A. With difficulty.
Q. With difficulty?
A. Yeah. I mean, it turned out that when you knew it -- after you knew it, you could go back and you can say "This is a new way to write a paper." You put a little -- a few little single word codes in it and say to someone "Can you find them?"
Q. Do you know why the study authors did not publish the second 6 months' worth of data?
MR. SAHAM: Objection, form.
A. How would I know why they did not? I would suspect that they didn't because I know Steven Geis and that he wanted to win, just like on the MUCOSA study. But the answer is: I don't know why they didn't. I know they should have, no matter what, or they shouldn't have to publish it. They've got to tell me it exists and they've got to tell me the results, because those are the results of their trial.
Q. (BY MR. DOUGHERTY) So, you're not offering any opinions in this case about whether the second 6 months

worth of data is valid or invalid; is that correct?
MR. SAHAM: Objection, form, foundation.
A. Say again.
Q. (BY MR. DOUGHERTY) You're not offering any opinions in this case about whether or not the second 6 months' worth of data is valid or invalid, correct?
MR. SAHAM: Objection, form, vague as to valid.
A. Now, my presumption would be before -- when I get the study, is that it was the study; and I get to see the study.
MR. DOUGHERTY: Can you read back my question, please?
A. Who decides it's valid or not.
MR. DOUGHERTY: Can you read back my question to him, please?
MR. SAHAM: Objection, asked and answered as the transcript indicates.
Q. (BY MR. DOUGHERTY) Answer the question, please.
A. I don't know the answer to that question.
Q. Well, this is the day to answer it.
THE WITNESS: Read me the question.
(Question read back for the record.)
MR. SAHAM: Objection, vague as to "valid," form, asked and answered.

A. And the answer to that that would be a -- I would have to depend upon the statisticians to tell me.
Q. (BY MR. DOUGHERTY) So, you're not offering any opinions on that issue in this case, correct?
MR. SAHAM: Same objections.
A. I have no personal opinion that I can derive without the help of the statisticians.
Q. (BY MR. DOUGHERTY) I want you to really just focus on my question, because I never want to hear you at trial talk about the second 6 months of data, unless you tell me today that you intend to talk to about the second 6 months worth of data.
A. (Witness shakes head.)
Q. Do you intend to offer any testimony in this trial about the second 6 months worth of data, "yes" or "no"?
MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.
Q. (BY MR. DOUGHERTY) If you're leaving that for another expert, fine. I just want to know what you're going to do?
A. I will not exclude the fact the study went for one year. If you ask me about the individual outcome, which is what you mean, the results of the study for one year, I will not testify as to that. I will testify to

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the fact that the study did go one year and it had results. Now, whether they are valid or not is for someone to discuss.

Q. So, you're not ruling out the possibility, Dr. Graham, that the second 6 months worth of data was invalid, correct?

MR. SAHAM: Objection, form, foundation.

A. I'm not ruling out whether it was valid or invalid.

Q. (BY MR. DOUGHERTY) Okay. And you have heard the reasons that the authors have given, right, for why they did not publish the second 6 months worth of data? You looked at those reasons as part of your assignment in this case or not?

A. I looked at that.

Q. Okay. Are you offering opinion about the validity of the reasons offered by the JAMA authors as to why they didn't publish the second 6 months worth of data or are you leaving that for somebody else?

A. Well, those are statistical questions, again, too.

Q. So, you're not going to testify about the reasons?

A. The actual reasons that they use, no.

Q. No. Your evaluation of those reasons, you're not

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going to evaluate those reasons in your testimony, correct?

MR. SAHAM: Objection, form, foundation, calls for a legal conclusion.

A. I'm not going to evaluate those reasons.

Q. (BY MR. DOUGHERTY) In the last sentence of your report or Paragraph 36 of your report, Dr. Graham, you say -- and I'll wait until to you get there so you can follow along with me.

A. Okay.

Q. I'm sorry, sir. If you could turn to the page prior and start at the bottom.

A. (Witness complies with request.)

Q. If -- I'm reading now from Paragraph 36: "If, for the sake of argument, one took the view that depletion of susceptibles occurred (and parenthetically I reject that notion) one would still need to justify why the second 6 -- why the 6-month data set was a valid representation of the study." Do you see that?

A. Yeah.

Q. So your parenthetical rejection of the depletion of susceptibles -- I'm just trying to -- because you didn't detail any of that in your report and I just want to confirm today that you are not going to offer any opinions in the trial of this matter on whether or not

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the depletion of susceptibles actually occurred and affected the second 6 months worth of data?

MR. SAHAM: Objection, form, foundation, incomplete hypothetical.

A. That is, again, a statistical question. I don't do that. But I will be willing to talk about the need to present the entire data set, et cetera, as it says in the next paragraph -- part of that paragraph.

Q. (BY MR. DOUGHERTY) Whether it's valid or invalid?

A. Whether it's valid or invalid.

MR. SAHAM: Objection, form, foundation --

Q. (BY MR. DOUGHERTY) Because Dr. David --

MR. SAHAM: Let me make my objection, John, so we have it on the record.

MR. DOUGHERTY: He's already answered the question.

MR. SAHAM: Well -- and I would --

MR. DOUGHERTY: Go ahead. Go ahead, Scott. I'll give you that courtesy. I'm sorry.

MR. SAHAM: -- I would caution the witness, Dr. Graham, the way this works, I need to make my objection so it can be ruled on. And we're all driving the court reporter crazy by talking over her. So if you could just pause so I can make my objection.

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And my objection to the last question was form, foundation, and assumes facts not in evidence.

Q. (BY MR. DOUGHERTY) Okay. So I want to make sure I know where we are. I think I've got it.

So in the rest of that article or the rest of that Paragraph 32 of your expert report -- or 36 of your expert report you say that -- and I think you've confirmed here today. You're not going to talk -- you're not going to testify in this case about whether or not the depletion of susceptibles occurred because in your opinion regardless of whether the second 6 months worth of data was good or not good, you believe that the JAMA authors should have included some statement in the article about the data at 12 months. Is that what you're saying?

A. They should have presented the study they did.

Q. That's a little bit different from what I asked you, Dr. Graham. So it's really important that we kind of nail this down.

All you say about the second 6 months of data here is that the entire data set, statistical or otherwise, and the reasoning must be presented along with the reasons for truncating the data. Do you see that?

A. "... for excluding less favorable data, and why a

subset analysis was being offered as a more representative analysis," right.
Q. Right. That's the opinion you want to offer?
A. Right.
Q. Okay. And you haven't actually looked at the second 6 months worth of data, correct?
MR. SAHAM: Objection, misstates prior testimony, assumes facts not in evidence, incomplete hypothetical, form, and foundation.
Q. (BY MR. DOUGHERTY) In other words, you don't know whether the second 6 months worth of data is valid or invalid?
A. I've looked at all the data. But the question about "valid" or "invalid" is a whole area of statistics.
Q. That you don't want to express on?
A. That I -- that I don't do.
Q. Okay. So you don't know -- when you say that the second 6 months worth of data excluded less favorable data, it would only be less favorable, Doctor, if that data was reliable and invalid, correct?
MR. SAHAM: Objection, form, foundation, assumes facts not found in evidence, and misstates prior testimony.
Q. (BY MR. DOUGHERTY) Right?

A. Only valid data is reliable.
Q. Okay. So, you can't say one way or the other whether not presenting the second 6 months worth of data excluded less favorable data because you can't express an opinion as to whether or not that second 6 months worth of valid is valid; is that fair?
MR. SAHAM: Objection, form, misstates prior testimony, assumes facts not in evidence.
Q. (BY MR. DOUGHERTY) Is that fair?
A. Sounds fair.
Q. And you'll abide by that for the rest of this case?
A. Probably.
Q. I can depend on you for that, can't I, Dr. Graham?
A. Possibly.
Q. You're not going to go back on your word on that one, are you?
A. Maybe.
MR. SAHAM: Objection, argumentative, misstates testimony --
Q. (BY MR. DOUGHERTY) You may? No, you won't?
A. (No audible response.)
MR. SAHAM: -- form, foundation.
MR. DOUGHERTY: You may indicate that the

witness has said "no."
Let's take a five-minute break, please.
THE VIDEOGRAPHER: We're now going off the record. The time is 2:39.
(Whereupon, a recess was taken from 2:39 p.m. to 2:56 p.m.)
THE VIDEOGRAPHER: We're back on the record. The time is, approximately, 2:56.
Q. (BY MR. DOUGHERTY) Dr. Graham, one of your previous answers you mentioned "Dr. Geis." Do you intend testify in this case about Dr. Geis?
A. I hope not.
Q. Do you intend to testify about the motivations or desires of anyone employed by Searle or Pharmacia as it relates to the CLASS trial?
A. I have no way of knowing what they were thinking. All I can know is what they did.
Q. But my question to you, sir, is: Do you intend to testify about the motivations of any scientists working for G.D. Searle or Pharmacia?
A. No.
Q. Do you intend to testify about the motivations of any of the JAMA authors?
A. No.
Q. Do you intend to testify about the actions of any

company scientist or JAMA authors --
MR. SAHAM: Objection to form.
Q. (BY MR. DOUGHERTY) -- in connection with the CLASS trial?
MR. SAHAM: Objection to form.
A. No.
Q. (BY MR. DOUGHERTY) And you're not going to testify about the reasons why they might have done this or that, correct?
MR. SAHAM: Objection, form.
A. I don't plan to; but, you know, I don't want to disappoint you. When we were discussing this 6-month data and I agreed that I wasn't going to discuss the validity of it, that's the statistical validity I focused on; but I'm still very set on the concept that they should have told the world about the entire data set and those statistical otherwise that I listed in this paragraph. So that's not that it's going to exclude 6 months' data, I'm just excluding the statistical validity of that data.
Q. But you're not going to offer any testimony about whether it was not -- whether or not it was reasonable for the JAMA authors and the company scientists to conclude that the data after 6 months were not reliable --

MR. SAHAM: Objection, form, foundation.
A. I --
Q. (BY MR. DOUGHERTY) -- putting aside the disclosure issue, sir?
A. Yeah, they should have told us that it existed and then explained to us why they thought it was excludable.
Q. I understand and I'm calling that the "disclosure issue," but I want to get back to the -- my question.
MR. DOUGHERTY: Madam Reporter, could you read it back, please?
(Question read back for the record.)
MR. SAHAM: Objection, form, vague as to "reasonable."
Q. (BY MR. DOUGHERTY) You can answer the question, Dr. Graham.
A. I don't see that that's different than what I said. That's statistical validity that they would base it on or at least -- and I'm not going to address the statistical validity of that data.
Q. You're not going to testify that it was unreasonable for them to have concluded that the second 6 months worth of data was not valid?
A. I'm not going to testify to that, but I will testify it was unreasonable that they excluded it.

Q. And just so that we understand the kind of --
A. Disclosure of it.
Q. Okay. Just so that we understand your disclosure rule that you're applying in this case, Dr. Graham, so that we can test whether or not you have applied it in your own life, is it your opinion that in publications of clinical trial data that the authors of that publication must always publish the full data set from the trial whether or not they believe all of it is valid or must explain why they are not discussing that data in the article?
A. I --
MR. SAHAM: Objection, form, foundation --
Q. (BY MR. DOUGHERTY) Is that your opinion?
MR. SAHAM: -- incomplete hypothetical.
A. That's, basically, my opinion. It's important never to mislead.
Q. (BY MR. DOUGHERTY) Well, you're not offering opinions in this case about whether anybody was misled, right, Dr. Graham?
A. Well, if you don't do that, then by my philosophy you're definitely "misleading" about what did you.
Q. You're not offering any opinions in this case or any testimony in this case, Dr. Graham, that anybody was misled by the JAMA article, are you?

A. Well, I personally know I was; but whether they intended that is another question.
Q. And you say that you were misled by the JAMA article because -- and I think you gave us some of the reasons, so let's make sure we have a complete list -- was the absence of a discussion of the 12-month data. Is that one of the things that you -- that caused you to be misled?
MR. SAHAM: Objection, form, vague.
A. I was misled in that the study was not described in a forthright manner, you know, "This is what we set out to do. This was our endpoint. These are our results."
Q. (BY MR. DOUGHERTY) Well, sir, I want to get as complete a list as possible, Dr. Graham, just so that the jury understands the basis for your testimony that you were misled by the JAMA article. So, can you just list for us the things that were either in the JAMA article or not in the JAMA article that caused you personally to be misled?
MR. SAHAM: Objection, form.
A. Do you want me to send you a list?
Q. (BY MR. DOUGHERTY) I want you to give us that list today.
A. Well, that -- I think that would not be

practical.
Q. Well, you better do the best you can, Dr. Graham, if you don't mind.
A. I'll state it again, that I would expect their article to tell me that this was the protocol, that this was the primary analysis, and these are the results and, then, to clearly identify what was the subgroup analysis, what was the post-hoc subgroup analysis, and so that I would understand where the data stood and how to analyze it.
I mean, many people, as you know, would say that you shouldn't even do the analysis after you fail on your original hypothesis or null hypothesis, but I would expect them to give me those data in a way that's very clear. And that would be the minimum.
Q. You said that many people say you don't even do an analysis once you've failed the primary endpoint; is that right?
A. That's one of the big arguments when people talk about subgroup analyses, whether you should even do them.
Q. But you don't agree with that, correct?
A. I think it's worthwhile to do the analysis and to be honest about what the results are.
Q. And, so, you believe it was fair for the JAMA

authors to present the analysis of the CLASS data that they felt was the most valid. Your objection to the way that they did it was the failure to disclose the primary endpoint and the fact that the analyses were post hoc and the fact that there was 12 months worth of data. Do I have that right?

A. That's reasonable.

Q. And Dr. Graham --

A. -- and the -- and either the 12 month data was less favorable with the proviso that they could explain why that's not valid.

Q. Okay. Anything else?

A. That's enough.

Q. All right. This is the chance to put it all in. Is that all you've got?

A. That's fine.

Q. I just don't want to hear any other explanations later, okay?

A. I'll try not.

Q. I'll hold you to that.

You would agree with me, Dr. Graham, that the results of the primary primary endpoint are disclosed in the JAMA article?

A. In retrospect, if you know what they are -- if you know the protocol, you can find it in there. It's

kind of a hidden code, but you can.

Q. Well, there's nothing hidden about it, Dr. Graham. You'd agree with me that they disclosed that the study was powered to look for ulcer complications, correct?

MR. SAHAM: Objection, form, assumes fact not in evidence.

A. The results of the study were that the analyzed incidence rates for upper GI complications were "bang-bang." That's the -- that is the outcome, all right? Everything else is subgroup.

Q. (BY MR. DOUGHERTY) And what P value did they assign to that outcome, Dr. Graham?

A. They assigned 0.9.

Q. So, they disclosed right there -- and you're pointing -- just --

A. No, they didn't disclose it that way.

Q. Let me finish my --

A. They disclosed --

Q. Let me finish my question, Dr. Graham, if you don't mind.

A. All right.

Q. Just so the record is clear, you're pointing to the abstract portion of the article?

A. Yeah.

Q. Okay. And ulcer complications were a primary primary endpoint of the CLASS trial, correct?

A. I know that, but I would not know that by reading the paper.

Q. And in the abstract itself on the first page of the article, the authors tell everyone who reads the article that as against ulcer complications there was not a statistically significant difference between Celebrex and the pooled NSAIDs, correct?

MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.

A. The -- what one would expect them to say is that the primary hypothesis was against these complications and we got this result, "period." And, then, we get a bunch of subgroup analyses and we found some interesting data. And we didn't, if you'd like, we didn't do corrections for multiple comparisons. But that -- I mean, that's what how you would say this in a scientific paper to be honest and not misleading or not potentially mislead.

And, so, when you read this, you get one P value that's a little off and then you start getting good P values and good comparisons. Now, that just has to be unusual way to present data.

Q. (BY MR. DOUGHERTY) Let me ask you this,

Dr. Graham: If someone reading the JAMA article wanted to answer the question as to whether or not Celebrex was statistically different from the pooled NSAIDs against ulcer complications, you would agree with me that the answer to that question is revealed in the abstract on the first page of the article by the disclosure of the .09 P value, correct?

MR. SAHAM: Objection, form, foundation, assumes facts not in evidence, incomplete hypothetical.

Q. (BY MR. DOUGHERTY) You can answer.

A. Only if you had read the protocol would you come away with -- that that was the answer to the study, that the study failed.

Q. That wasn't my question, Dr. Graham.

A. They didn't ever tell me what the question was.

Q. No. Let's focus on my question for a second --

A. Right.

Q. -- okay?

You would agree with me that in the abstract right on the first page of the JAMA article if someone wanted to know whether the CLASS study showed Celebrex being statistically significantly better than the pooled NSAIDs against ulcer complications, that the answer to that question is right there in the abstract on the first page; and the answer is "It is not statistically

significant because we disclosed a .09 P value"? You would agree with me, correct?
MR. SAHAM: Same objections.
Q. (BY MR. DOUGHERTY) That is right -- stated right there on the front page?
MR. SAHAM: Same objections.
Q. (BY MR. DOUGHERTY) That question is answered, is it not?
A. That answer is answerable on the first page if you know the question.
Q. But the question as against ulcer complications, putting aside whether or not you have to read further to find the primary endpoint, if the practitioner simply wanted to know whether or not Celecoxib is statistically significantly better than the pooled NSAIDs on the ulcer complications, that question, you would agree with me, is answered right there on the first page?
A. Well, then, I'll read the "conclusion."
Q. Just answer my question first.
A. But I'm saying I can go -- if you have set little codes for me like people doing Easter egg hunts and you say "Can I go look and find an Easter egg here and can I go find one there" and the answer is "yes," if I know that I'm looking for Easter eggs.
Q. Dr. Graham, I think -- and I'm going to ask you

the question again because --
A. And I'm going to give you the same kind of answer.
Q. I just -- I want to have a sense of mutual respect here, Dr. Graham: If a doctor wanted to know whether or not Celebrex was statistically significantly better than the pooled NSAIDs on the question of ulcer complications, you would agree with me that the answer to that is on the first page of the JAMA article, correct?
MR. SAHAM: Asked and answered.
A. Yeah, it says right here -- (witness pointing) -- it says "In this study, Celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard doses." That's what it says.
That's the conclusion that you take home from the message from this paper. That's the conclusion statement. "The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly." I mean, you read the conclusion for the conclusion. That's where I get it.
Q. (BY MR. DOUGHERTY) I'm focusing on the "Results"

section, Dr. Graham.
A. You're focusing saying there's a P value stuck in there that I can take out of the context of the rest of it and make meaningful and knowing what I know, yes, I can do that. At the time, no.
Q. But when you saw a P value in the "Results" section that was greater than .05, wouldn't that tell you that this study failed to prove Celecoxib was statistically significantly better?
A. And that's why the conclusion says that it is associated with a lower incidence to say "We failed on a study and we only could do some subgroups."
Q. Earlier today you said that the only -- from the vantage point of your experience in the field that the only clinically relevant endpoint are ulcer complications?
A. Absolutely.
Q. And, so, a sophisticated person like you, Dr. Graham, who wants to know "how did this study do against ulcer complications" would be able to tell by doing nothing more than reading the "Results" section that against what you have defined as the most clinically important endpoint "Celebrex failed," right?
MR. SAHAM: Object to form.
A. I didn't at the time and I haven't read this

editorial in a couple of years. We could go back and see if the editorial picked it up.
Q. (BY MR. DOUGHERTY) We're talking about the JAMA article?
A. And we're talking about the editorial to the JAMA article. Did they pick it up that they failed?
Q. (BY MR. DOUGHERTY) You testified earlier today that ulcer complications are the only important measure of GI safety in a study like this and that the rest is noise. Those are the words that you used, correct?
A. Well, not in all those words. I like it. I should have said that, if I didn't.
Q. Okay. And, again, it's obvious to you that --
A. Today.
Q. Well, did you not see the .09 or appreciate what .09 meant, Dr. Graham?
A. I didn't appreciate it in the context of an abstract. In fact, I'm sure there are many papers -- several papers of mine written said that this was a successful study.
Q. But, Dr. Graham, let's make sure that you're not having it both ways because you, again, took the position earlier today rather strongly -- I don't agree with it, but it's your opinion -- that complicated ulcers are the only clinically relevant information to

come out of this kind of a trial and that the rest is noise.

And so when you read the "Conclusions" section, Doctor, when it's talking about the combination of symptomatic ulcers and ulcer complications, you would have ignored that because it's just noise, right?

MR. SAHAM: Objection, form, foundation.

A. I should have.

Q. (BY MR. DOUGHERTY) Would there be any reason for you to even read any further in this article, given the position that you've taken for the purposes, presumably of this litigation, that anything other than ulcer complication is noise? There would have been no reason for you to read further, correct?

MR. SAHAM: Objection, form.

A. There should have been no more reason for me to read further, you know, that -- unfortunately, we are -- we tend to trust what our colleagues do, thinking that it's always in good faith and it's been peer-reviewed and the data are reliable and we can take it to the bank and just read it and kind of see, you know, how interesting it is. As it turns out, that this is not one of those papers.

Q. (BY MR. DOUGHERTY) Well, I challenge you on that a little bit further, Dr. Graham. If you'd just turn to

the article and go to Figure 2 --

A. Where at?

Q. -- which presents --

MR. SAHAM: Could you -- if we're going to talk about the article, could you give me a copy?

MR. DOUGHERTY: Oh, Scott, of course. I didn't realize you didn't carry one around in your back pocket. Here, take mine.

MR. SAHAM: I'll give it back. I gave the court reporter the extra one.

Q. (BY MR. DOUGHERTY) It's the JAMA article that has been marked previously in this litigation as Exhibit 3.

MR. DOUGHERTY: Is that right, Scott?

MR. SAHAM: Yeah, Wolf Exhibit 3.

MR. DOUGHERTY: Wolf 3.

Q. (BY MR. DOUGHERTY) So, let's take a look, Doctor, in light of the position you've taken in this case that complicated ulcers are the only important thing to look at. Why don't we look at where the results of the study are presented in Figure 2. Do you understand, Doctor, that Figure 2 contains three different charts, Dr. Graham?

A. I can see Figure 2, yes.

Q. And do you understand that the three different

charts present the ulcer complication data on the left and the symptomatic ulcer is an ulcer complications combined on the right?

A. Right.

Q. Do you see that? And, so, a person like you, a gastroenterologist, could have easily looked at Figure 2, Table A and seen all patients against ulcer complications shows a lack of statistical significance, right?

A. Yeah, but you're saying what I could have done, not -- and maybe what I should have done, but not what I did do at the time.

Q. And isn't it --

A. And that's a fact. You know, I stuck with what I did at the time and life's like that.

Q. But isn't it true, Dr. Graham, that the reason that you didn't stop reading the JAMA article at the time is because you were actually quite interested in what the data showed beyond the measure of simple ulcer complications and that you're only taking the position now that ulcer complications are the most important because you've been retained as an expert in this case?

MR. SAHAM: Objection, form, foundation, argumentative, assumes facts not, incomplete hypothetical.

A. I think I can show you papers of mine going back for 15 years that makes that same point.

Q. (BY MR. DOUGHERTY) Makes what same point?

A. That the only significant correlate is ulcer complications and everything else is irrelevant.

Q. So it would have been really simple for you, based upon just the two things that we've seen so far, for you to consider this JAMA article to be just noise because the authors were pretty clear that against the only endpoint that you think is clinically relevant Celebrex did not prove statistical significance, correct?

MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.

A. I had bought into the hypothesis, like many had, and, you know, we got to see the data presented before the paper appeared, et cetera, and learned about it. And I would say that when the paper came out, you skimmed it and kind of accepted what they tell you and --

Q. (BY MR. DOUGHERTY) Did you accept that they had told you that they were -- that the -- against ulcer complications that it was not statistically significantly better?

A. They didn't make it clear -- clearly that -- what

the protocol was, nor the fact that they had failed to meet their objective and that they were now, you know, data dredging subgroups in order show the data in the best possible light.
Q. All right. But for a man who believes that only ulcer complications -- that ulcer complications are the only important data, you would agree with me that the JAMA article clearly displays the results against that measure, correct?
A. That's not -- you used the word "clearly," but it -- the data can be identified within the paper.
Q. All you've got to do is look at Figure 2, right, even if you don't read the abstract, "agreed"?
A. You can find the data.
Q. It's not hidden like an Easter egg here in Table 2. It's actually the first set of bars in that entire table, isn't it?
A. It's -- you show the table. It's there, self-evident.
Q. It is self-evident, isn't it?
A. Once you look for it.
Q. Well, you would be looking for it because you're the guy that thinks that's the only thing worth looking for, right?
A. Right.

Q. So, it wouldn't have been hard for you to find, would it?
A. Must have been.
Q. "Must have been"? I'm trying to understand. Are you --
A. I mean, I could find you papers where I misquoted this paper.
Q. Papers that you wrote that misquote this paper?
A. Yeah, the outcome.
Q. In fact, you've written papers that focus on the combined endpoint, do you not?
A. On what endpoint?
Q. The combined endpoint of symptomatic ulcers and ulcer complications?
A. Only to say bad things about them, never to say positive things about them. And I can show you those papers going back for years, showing that that's a bad thing. The only primary endpoint that counts is A, B, C.
Q. So why would you even spend any time reading an article that's --
A. I didn't spend a lot of time or effort. It's just a hypothesis.
Q. Let me finish the question. Why would you spend any time reading an article that, according to you, your

own writings have rejected a combined endpoint and the article is self-evident, that it didn't meet the primary endpoint? Why would you spend any time reading this?
A. How do I know what the primary endpoint is? It says here --
Q. Well, the only important primary endpoint --
MR. SAHAM: Let him finish his answer.
Q. (BY MR. DOUGHERTY) -- the only important primary endpoint --
MR. SAHAM: Let him finish. You cut him off. Let him --
Q. (BY MR. DOUGHERTY) All right. Go ahead.
A. I mean, I read you the conclusion. It says Celebrex at dosages greater than, et cetera, et cetera. It's a very positive article.
Q. But you believed these complicated ulcers are the only reliable endpoint, correct?
A. I believe that and so does the FDA, unfortunately, for them.
Q. You believe that these CSUGIE's here are the only reliable endpoint, correct?
A. I think they are the reliable endpoint, to distinguish one from another, yes.
Q. Is it your testimony in this case that you only read the conclusion of the JAMA article?

A. I don't remember what I read at the time.
Q. Are you going to testify about your recollections of reading the JAMA article in this case?
A. Not unless you ask me.
Q. You don't intend to testify about that?
A. My testimony is going to be related to Dr. Wang's testimony.
Q. So, let's just go through this again. You believe that these CSUGIE's are the only reliable endpoint?
A. I think that the main problem with NSAIDs is bleeding, perforation, and obstruction; and that for someone to have a safer drug, it has to show that it has a significant effect preventing those complications.
Q. And your recollection is that -- well, you're not sure what part of the JAMA article you read or whether you read it all; is that fair?
A. That's fair.
Q. And, so, after this was published in the year 2000, Dr. Graham, you knew that this big study had taken place, correct?
A. We knew -- I knew that the big study had taken place and they were out presenting it all over.
Q. Well --
A. Dr. Goldstein was going around the world giving

talks.
Q. Well, are you going to testify about those talks in this trial?
A. No.
Q. Are you going to talk about -- or testify about any of the company's presentation of the CLASS data, other than what's in this JAMA article?
A. No.
Q. And you understood even before the company presented the results of the CLASS trial -- I'm assuming you knew the CLASS trial was going on, didn't you?
A. Everyone knew the CLASS trial was going on.
Q. And it was pretty unprecedented in terms of the number of patients they had in there, correct?
A. Well, it wasn't unprecedented. We'd already done the MUCOSA trial which had lots of patients. I mean, this had a big number of patients because they needed a big number of patients to show small differences.
Q. Did you know before the JAMA article was published that there was a big number of patients in the CLASS trial? Did you know how big it was?
A. I'm sure it was presented here and there, what they were doing --
Q. And --
A. -- but you just assume it's a lot.

Q. -- were you eager to see the results of the CLASS trial?
A. Well, I -- in the VIGOR trial, everybody was very interested in what was going to happen to those.
Q. And you personally were very interested?
A. Yes.
Q. And when the results of the CLASS trial were presented, did you have to wait to read the JAMA article to know that the study had not proven statistical significance on complicated ulcers?
MR. SAHAM: Could you read that back?
(Question read back for the record.)
MR. SAHAM: Objection, form.
A. When I learned that the study had failed was when the FDA made their announcement.
Q. (BY MR. DOUGHERTY) In 2001?
A. Whenever that was.
Q. February 2001?
A. Right.
Q. So, you knew that this big trial was going on. You knew the VIGOR trial was going on. You were eager to see the results. And you're testifying here today under oath that you didn't know the results of the CLASS trial until February of 2001 when the FDA released its commentary on the results?

A. I was not aware that it failed, no.
Q. That's not my question.
Are you testifying here today under oath that you didn't know the results of the CLASS trial against complicated ulcers prior to the FDA's disclosures in February of 2001?
A. I just said I did not know that it had failed until the FDA made their disclosure.
Q. So, you were not part of any discussions at professional meetings or otherwise discussing the results of the CLASS trial and the fact that it had failed against ulcer complications. You were not part of any of those discussions between March of 2000 and February of 2001?
A. I was out of the NSAID business.
Q. You were out of the NSAID business?
A. Right.
Q. But you were still treating patients on NSAIDs, correct?
A. Well, some.
Q. And you were treating patients, Doctor, who presented to you with ulcer complications as defined in the CLASS trial, correct?
A. Well, yeah, we see lots of bleeds.
Q. And is it your testimony here today under oath

that you were unaware of the performance of Celecoxib and the other NSAIDs in the CLASS trial on the issue ever complicated ulcers or CSUGIE's until February of 2001?
MR. SAHAM: Objection to form, foundation.
A. I was aware of the aspirin data, that aspirin had negated the effect.
Q. (BY MR. DOUGHERTY) Is it your testimony here today under oath that you were not aware of the primary endpoint of complicated ulcers until February of 2001?
A. Right.
MR. SAHAM: Objection, form, foundation.
Q. (BY MR. DOUGHERTY) Is that what you're saying?
A. That's what I said, so you can read it back whenever you want to hear it again.
Q. When you say you were out of the NSAID business, I want to make sure I understand that. Did you not attend any professional meetings or conferences of other gastroenterologists between March of 2000 and February of 2001?
A. Of course, I attended those.
Q. And wasn't the CLASS and VIGOR trials a subject of discussion at those conferences?
A. They were often presented, yes; and they were typically presented by the spokesperson for the

companies at that time and with a very positive spin, first announcing typically they had no conflicts of interest, but not in what I would call, in retrospect, a reasonable way. I mean --

Q. But you didn't --

MR. SAHAM: Let him finish his answer.

Q. (BY MR. DOUGHERTY) Yeah, go ahead. Go ahead. I didn't mean to cut you off.

A. Back in the Misoprostol days, I was one of the spokespersons for Misoprostol. But when they went with a different company Pharmacia, they decided they didn't need my services because they couldn't control what I said.

Q. Did you know, Doctor, before the JAMA article was published that the CLASS trial was looking at the question of complicated ulcers?

A. Well, they knew that it was modeled on the MUCOSA trial.

Q. I'm not sure that helps answer the question, Doctor.

A. The MUCOSA trial looked at complicated ulcers. It was the first one, the only one.

Q. So, you knew that -- even before the JAMA article was published, you knew that there was a trial out there involving Celebrex and looking at the question of

complicated ulcers, but that you didn't know the results of that trial until February of 2001?

A. I knew the positive results. I knew the aspirin, et cetera, and the nice beautiful curves that they like to show. I mean, they show that stuff all the time. But if they had presented upfront that "We did a study. These were the criteria and the outcome and we failed on that and all we're going to show you is some odd subgroup analysis," they wouldn't have sold 50 dollars more of the drug.

Q. Do you want the jury to believe, Dr. Graham, that you knew that the CLASS trial was looking for complicated ulcers and that you believed that that is the only measure of interest in a trial like the CLASS trial and that you never asked the question between March of 2000 and February of 2001 "How did Celebrex do against complicated ulcers"? Is that what you want the jury to believe?

MR. SAHAM: Objection, form, foundation, incomplete hypothetical, assumes facts not in evidence.

A. Sure, they believe what they'd like to believe. If you remember, we're dealing with a very positive hypothesis. We have two studies, two drugs that are running against each other, both have the same hypothesis. The VIGOR study says, you know, "We won."

They say, if you like, "We won."

And that says the hypothesis is true -- may be true, that COX-2 inhibitors are safer; and there are probably a thousand papers out there that say that the side -- that the events in COX-2 inhibitors are 50 percent of that of traditional NSAIDs. And there are still papers being written that way. And they're not written that way because the data was cleared, God and everybody, from those -- this study and the other study. They came out, you know, very similar times and similar results and seemed to confirm the hypothesis.

Q. Did you know the results of the VIGOR trial before it was published in the New England Journal of Medicine?

A. Did I see them before or after? "I don't know."

Q. Did you read the New England Journal of Medicine article at the time it came out?

A. Right.

Q. You did?

A. I read the New England Journal article -- at least looked at the New England Journal article when it came out.

Q. And did you know what the endpoint was from reading the New England Journal of Medicine for the VIGOR trial?

A. The New England Journal article explained the endpoints.

Q. And why did you read the article?

A. I read the article because it's one of those things of interest.

Q. Why would it be of interest, Dr. Graham, when the endpoint that was being studied in the VIGOR trial was a combined endpoint of complicated --

A. I didn't agree --

Q. -- and symptomatic ulcers?

A. I don't agree, necessarily with them; but I read them.

Q. Oh, so, you would have continued to read even though the endpoint being studied was not just complicated ulcers?

A. Well, you're going to read it, anyway.

Q. Are you testifying here today under oath that you are interested in reading the results of a paper even if the trial being discuss in that paper did not have a primary endpoint of complicated ulcers, but had a composite endpoint like VIGOR?

A. My wife says I'm a pathologic reader, which means I read cereal bowls and anything around. And, so, I read, you know. It's just what we do in medicine.

Q. Are you -- do you want the jury in this case to

believe, Dr. Graham, that you were in the dark until February of 2001 on whether CLASS had shown a statistically significant advantage for Celebrex over the pooled NSAIDs on complicated ulcers?
A. Can you --
Q. Do you want the jury to believe that you were in the dark on the answer to that question until February of 2001?
MR. SAHAM: Objection, form, vague.
A. They can believe that until the FDA came out with their data I felt that this was a positive study, that they had, if you like, at least, in part, confirmed the hypothesis. It wasn't a perfect study -- there's no perfect studies -- but that's what I believed.
Q. (BY MR. DOUGHERTY) If you were out of the NSAID business at the time that the JAMA article was published -- well, let me ask you something, Dr. Graham: Do you actually remember ready reading the New England Journal article on the VIGOR trial?
A. I remember having it -- I mean getting copies, yes. I don't know if I sat down and read every single word, but I know that I got copies. I mean, you could not get -- not get copies because these two articles they were coming to your office every day and giving you things and drugs, et cetera.

Q. Were you treating patients between March of 2000 and February 2001?
A. I've treated patients for -- every day for years.
Q. Did you owe your patients an obligation to actually find out the answer to the question of whether or not CLASS had proven Celecoxib being statistically significantly better on ulcer complications than the other NSAIDs? Did you owe that to your patients to know the answer to that question?
MR. SAHAM: Objection, form, incomplete hypothetical, foundation.
A. I don't think so. I mean, I don't use -- I don't treat patients that require NSAIDs. And when they do require NSAIDs, I take them off of NSAIDs because they've had a complication.
Q. (BY MR. DOUGHERTY) You take them off because NSAIDs are toxic, right?
A. No, because I see the patients with the complication. So what I do is take them off of NSAIDs.
Q. I'm just finding it difficult, Dr. Graham, to accept your testimony that you did not know the results -- the ulcer complication results of CLASS until February of 2001.
A. I --
Q. Are you standing behind your testimony, sir --

THE WITNESS: Do you want to read him some of my answers (asking court reporter to read back)?
Q. (BY MR. DOUGHERTY) Do you -- let me just finish my question, Dr. Graham.
A. This is the last time I'm going to answer same question, okay? You can ask it more, but you got one answer and that is: I agreed that I did not in that time period. And you can ask it 4 more times or 25 more times and you're going to get the same answer.
Q. So, you didn't know until February of 2001?
A. I did not know it had failed until the FDA presented their data.
Q. And do you want the jury to believe, Dr. Graham, that between March of 2000 and February of 2001 when you're listening to the presentation of the CLASS data and for a guy who claims that ulcer complications is the only thing of interest that you didn't raise your hand and ask the question "How did you do against ulcer complications"? Is that what you want the jury to believe?
MR. SAHAM: Objection, form, foundation assumes facts not in evidence incomplete hypothetical.
Q. (BY MR. DOUGHERTY) Is that what you want the jury to believe?
MR. SAHAM: Same objections.

A. And you've had my answer to all these questions. You can take it as many times as you want. Do you want to read him back my answer (asking the court reporter to read back)?
Q. (BY MR. DOUGHERTY) Is that what you want the jury to believe, that you never asked?
MR. SAHAM: Same objection.
A. You know, if I had asked, that I would remember; and I'm the nasty guy that asks questions like that.
Q. (BY MR. DOUGHERTY) You are.
A. Yeah --
Q. You have a reputation --
A. -- right.
Q. -- for being a bit of a -- what's the right word?
A. Any one you like.
Q. "Provocateur"; is that fair?
A. Could be, could be.
Q. Would you agree that you've been characterized that way?
A. I've been asked -- I ask difficult questions --
Q. So, here we have a gentleman --
A. -- but I tend not to go to places where -- I go to the national meetings and I hear what they say. But where the down and dirty stuff is that the drug companies are putting on, dinners and symposiums, I

don't go to those.
Q. Dr. Graham, here's what I'm -- here's my question to you, sir --
A. If it's the same question, the answer's the same.
Q. Why don't you give me the courtesy of letting me ask the question?
A. Well, why don't you give me the courtesy of asking a different question?
Q. I'm just trying to explore --
A. I gave you the answer --
Q. -- the plausibility of your answer.
A. -- and the jury can believe whatever they want. Those are the facts.
Q. So, at none of these conferences or presentations did you ever ask a colleague or the presenter, even though you have a reputation for being a provocateur, you never asked how the CLASS trial did on the ulcer complications; is that true?
MR. SAHAM: Objection, form --
Q. (BY MR. DOUGHERTY) You never asked?
MR. SAHAM: -- form, foundation, assumes facts not in evidence, incomplete hypothetical.
A. I have no memory of any asking like that. Remember, I'm an HP guy.
Q. (BY MR. DOUGHERTY) You testified that your take

away from the CLASS presentations was positive. Are you saying that you didn't actually try and get behind those presentations at all?
MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.
Q. (BY MR. DOUGHERTY) I mean, you're not saying that you were gullable and were duped by anything, are you?
MR. SAHAM: Same objections, argumentative.
A. I must have been.
Q. (BY MR. DOUGHERTY) Really? Is that your testimony, that you must have been -- a smart guy like, a provocateur, a guy who knew that these results were out there, that you were fooled?
MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.
I think we've got to change the tape, John.
MR. DOUGHERTY: Yeah.
MR. SAHAM: Is this a good break time?
THE VIDEOGRAPHER: This is now the end of tape No. 4 of the deposition of Dr. David Graham. We're off the record. The time is, approximately, 3:40.
(Whereupon, a recess was taken from 3:40 p.m. to 3:51 p.m.)
THE VIDEOGRAPHER: We're now back on the

record with tape No. 5 of the deposition of Dr. David Graham. The time is, approximately, 3:51.
Q. (BY MR. DOUGHERTY) Dr. Graham, you testified that you had some recollection of attending conferences or other talks where the CLASS data was presented prior to February of 2001; is that right?
A. Yes.
Q. And that your recollection of those presentations was that the outcome of the trial was, generally, positive; is that correct?
A. Yes.
Q. And, Doctor, do you remember whether those presentations were presenting the combination endpoint of complicated ulcers and symptomatic ulcers?
A. Presumably so. I mean, they would present the data, at least, as presented in the paper by the pharmaceutical company. Most of them were probably using pharmaceutical company slides.
Q. But, Dr. Graham, you've already testified in this case that you don't believe that symptomatic ulcers and ulcer complications combined is a relevant endpoint to study, correct?
A. Right.
Q. So, given the fact that you have a recollection of being at presentations where the results of one of

the largest clinical trials ever done on the question of NSAID versus COX-2's gastrointestinal safety that you took away a positive message even though they were presenting an outcome that you don't even believe is relevant. Is that what you're saying?
MR. SAHAM: Could you read that back? Sorry.
(Question read back for the record.)
MR. SAHAM: Objection to form.
A. Yeah, they were focused particularly on the aspirin/non-aspirin story and show that the aspirin/non-aspirin users, the drug, you know, looked, if you like, wonderful. They didn't bother to tell me that in the 6-month data that looked wonderful; and the year data, it looked not wonderful and that that went away. But that was what the FDA had to tell me, too, that the positive things -- the really good-looking positive things disappeared over time. But they're very good about giving a positive spin on the data.
Q. (BY MR. DOUGHERTY) My question to you, though, is, sir: When you were at the presentations of the CLASS data before February of 2001 and you took away a positive impression, you were taking away a positive impression of presentations on a combined endpoint that you believe was not relevant, correct?

A. I don't know what -- I mean that I would take away a positive impression, which is an impression of what they said and what -- you know, did the study work and did they have positive data. And I don't think I was looking at it or caring so much at the time about the individual aspects of the presentation.

I wasn't -- the real question was "were you using the drug" and "almost never"; and the other question was "which one was the better choice, Celecoxib or Rofecoxib" and that was the big argument in the world, is which one was the superior drug, not only in the -- since they both said they were safe and had some benefit for patients with -- taking NSAIDs compared to the others.

And it came down to other issues like Rofecoxib causing hypertension and edema, kidney changes much more commonly than Celecoxib. And, of course, they had Bextra at the same time, too. So, it's a complicated time when everybody's bringing out new things and we're hearing about Lumiracoxib and other drugs. So this was a time that this was going to be the solution to our problems.

Q. So for a guy like you when you're hearing presentations and there's a bunch of data coming out all around the same time, wasn't that the time for you to

actually start paying attention to those results?

MR. SAHAM: Objection, form, foundation, incomplete hypothetical.

A. Not particularly.

Q. (BY MR. DOUGHERTY) And, so, it's true that you weren't actually paying careful attention to what the results were that were being presented before February of 2001 about CLASS?

A. I was paying attention to them. And it's like any other gastroenterologist or like a gastroenterologist with a more special interest in the area; but, I mean, it wasn't one that I was going to go out on the road and talk about and have to be the world's expert.

Q. In fact, you actually did nothing, Dr. Graham, to investigate the results of the CLASS trial prior to February of 2001; is that correct?

MR. SAHAM: Objection, form, foundation --

A. I don't understand the question.

MR. SAHAM: -- assumes facts not in evidence.

Q. (BY MR. DOUGHERTY) You didn't do anything to investigate the results of the CLASS trial prior to February of 2001; is that fair?

MR. SAHAM: Same objection.

A. I don't know what I would do to investigate them.

Q. (BY MR. DOUGHERTY) Ask questions, write the company a letter, pull aside a colleague, ask a question about how they did against the only endpoint that you considered to be relevant. You didn't do any of that; is that right?

MR. SAHAM: Objection to form, foundation.

A. It's a long time ago. I don't know what I did. I know I had a lot of their drug people come see me, but they would -- they had their spiel.

Q. (BY MR. DOUGHERTY) So, the answer to my question is you didn't do anything?

A. I didn't do anything special.

MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.

Q. (BY MR. DOUGHERTY) You didn't do anything special, which leads you to testify that it was only in February of 2001 that you learned what the results were versus ulcer complications; is that right?

MR. SAHAM: Same objection.

A. I'd say that in 2001 I learned that the FDA did not agree with their analysis and felt that -- at least presented that the data they -- the analyses they presented were incomplete or inaccurate and that they weren't going to get their hope for elimination of the

exclusion based upon CLASS labeling.

Q. (BY MR. DOUGHERTY) "Their hope for," the company's hoped for; is that what you're saying?

A. Yes. I mean, that was the whole goal to put this money into it, is to get that exclusion removed.

Q. Are you going to be offering any testimony in this case about what the company's goals were with CLASS?

MR. SAHAM: Form, foundation.

A. I don't think the company hid it. That's the reason that they were doing the study, is to get rid of the CLASS labeling.

Q. (BY MR. DOUGHERTY) Are you going to be testifying at the trial in this matter about what the company's goals were with CLASS?

A. I would give -- I would testify if someone asked me what my impression was, but I don't know what -- I was not privy to their internal documents and their discussions. But they're certainly not crazy and that's what they needed.

Q. How did the presentations that you heard on the CLASS data or the JAMA article affect your practice as a gastroenterologist, if at all?

A. It didn't.

Q. So none of the data presented either in the JAMA

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article or at any of the presentations that you attended had any impact on the way that you practice medicine; is that correct?
MR. SAHAM: Objection, form, foundation.
A. Not that I -- not that I think, no.
Q. (BY MR. DOUGHERTY) Dr. Graham, you have read the final study report that was submitted to the FDA in June of 2000?
A. Not every word, no.
Q. But you looked at the tables in there and you looked at the comparison between the 6-month and 12-month data; is that fair?
A. I looked through the data that was in it, and I looked at the FDA person's analysis.
Q. Okay. And, so, you were able to see the results at 12 months, correct?
A. I was able to see the results at 12 months.
Q. Okay. Is it fair to say that the results at 12 month, also, didn't impact your practice of medicine in any way?
MR. SAHAM: Form, foundation.
Q. (BY MR. DOUGHERTY) Go ahead.
A. No -- I mean, it didn't change what I do. I don't deal with that kind of patient.
Q. So looking at the 6-month data in the JAMA

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article didn't affect your practice of medicine one way or the other and looking at the 12-month data later, again, didn't affect your practice of medicine one way or the other; is that fair?
MR. SAHAM: Objection, form, foundation.
A. It made me increasingly leery of what Pharma does and the honesty that comes from Pharma.
Q. (BY MR. DOUGHERTY) Doctor, if you can answer my question, please.
A. It affects my practice of medicine to have a diminished opinion of the people who are telling me things and what they write and the papers they give me.
Q. Dr. Graham, I want you to look at me or look at the camera, but just look up and answer this question: Do you want the jury to believe that looking at this 12-month data affected your practice of medicine, but looking at the 6-month data did not?
MR. SAHAM: Objection, asked and answered.
A. The 6-month data, if we go back again to the fact that this was a great hypothesis, the data suggested the hypothesis was going to be true. The 6-month data went along with the hypothesis may be true that asked for data which was this, if you like, ad hoc/post-hoc subgroup analysis seemed very reasonable; and, then, you start having that disappear.

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Q. (BY MR. DOUGHERTY) Did the 12-month data impact the way that you practiced medicine, Dr. Graham --
MR. SAHAM: Objection, asked and answered.
Q. (BY MR. DOUGHERTY) -- "yes" or "no"?
A. Very little affects the way I practice medicine.
Q. So, the answer to my question is seeing the 12-month data did not affect the way you practice medicine, correct?
MR. SAHAM: Objection, misstates prior testimony, asked and answered.
Q. (BY MR. DOUGHERTY) You can answer the question, please.
A. I would think that if they had gotten the best possible result that would also not have influenced the way I practice medicine.
Q. So, the answer to my question for the third time, Dr. Graham, is: The 12-month data did not impact your practice of medicine, correct?
A. Either way, right.
Q. Your report, Dr. Graham, talks a lot about the -- a lot about endoscopic ulcers, right?
A. Yes.
Q. And you'd agree with me that the endoscopic -- that endoscopic ulcers are different from symptomatic ulcers confirmed by endoscopy, correct?

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A. No.
Q. You think those are equivalent?
A. I make the point that you can have ulcers in patients with symptoms and you can have endoscopic ulcers in patients with symptoms; and that in these kind of studies, it's impossible to tell if it's a real ulcer or an endoscopic ulcer. And it's even more difficult here because what an endoscopic ulcer was or a real ulcer were not defined.
Q. So, for purposes of your opinions in this case, you're treating symptomatic ulcers and endoscopic ulcers as the same?
A. I'm treating symptomatic ulcers as a form probably of mostly endoscopic ulcers.
Q. Dr. Graham, if you could pick up your report, please?
A. Got it.
Q. If you could turn to Page 11 of your report.
A. (Witness complies with request.) Okay.
Q. On Page 11, you're talking about symptomatic ulcers and you're also talking about endoscopic ulcers. And if you go from the top of the page, third line down, you say "Clinically symptomatic ulcers are a fourth but very problematic type of upper GI NSAID-induced complication." Do you see that?

A. Right.
Q. And, then, you go on to describe why you think they're problematic; and we'll get to that in a second.
But just for purposes of establishing a common vocabulary with you or a common understanding, is it your opinion that clinically symptomatic ulcers are a type of upper GI NSAID-induced complication?
A. Can be.
Q. They can be. And in your practice are they?
A. Can be. Yeah, I see those.
Q. And it's not unreasonable for somebody to assume that a clinically symptomatic ulcer is a type of upper GI NSAID-induced complication, correct?
A. Correct.
Q. And it's not unreasonable for somebody to draw the association between NSAID use and a clinically symptomatic ulcer, correct?
A. Well -- and this is when you get wishy-washy or difficult. I pointed out earlier when they were first starting these studies they had put together an advisory group and one of the gurus of NSAID damages, Mike Langman, and Mike said and his group said -- he was working for Merck at the time, I think -- said "how do we tell whether an ulcer, a symptomatic ulcer is clinically relevant or whether it's one of these trivial

things?"
And, so, he said "I'm going to it on size." And he did it on ulcers that, I think, were 3 centimeters in the stomach and 2 centimeters in the duodenum and said that would be a reasonable approach in order to identify something that would have clinically significance -- clinical significance and medical significance. That wasn't taken up by any other companies.
Now, traditionally after that, it was decided that an ulcer was 3 millimeters with so-called apparent depth and that wasn't -- that could be 3 millimeters by half a millimeter -- and that 3 millimeter definition actually came from -- the FDA got stuck with this one -- a study I think with Cimetidine, an old Cimetidine study that they wanted to approval for 400 milligrams twice a day because Ranitidine had a BID indication. They had a four times a day indication and they knew their drug was very weak.
So the product manager made up a new definition of ulcer of 3 millimeters; and he got the FDA to accept it, which stuck the FDA with a 3 millimeter ulcer. So, you'd say what is the absolute minimum definition of an ulcer; and it would be 3 millimeters with apparent depth. Now that's a very, very weak

definition; and it's going to -- if you look in my atlas, it shows you how that can be wrong, many, if not most of the time.
This study had no definition for what an ulcer was or whether -- the definition of a symptomatic was "it was an ulcer you found." Any ulcer you found by definition was symptomatic; otherwise, you want to look at whatever the symptoms were. They could have been rectal bleeding. It still would be a symptomatic ulcer.
Q. But they only looked when there was a symptom in the CLASS trial?
A. Rectal bleeding was the symptom that you would look.
Q. But they only looked when there was a symptom?
A. But rectal bleeding would not be a symptom that you would say would be a symptomatic ulcer, but it would fit your definition of a symptomatic ulcer. So, it wouldn't be a symptom of the ulcer. It would be a symptom and an ulcer. It just happened to be the way it works out.
So I'm saying that they made a lot of those kind of mistakes by not making definitions. Be that as it may, this is what we're talking about here. So when you say to yourself "symptomatic ulcer," you're thinking something of a size and an importance. And when I see

one, I'm seeing a great big nasty ulcer that God and everyone would call an ulcer in a patient with symptoms. That is a complicated ulcer with symptoms.
A 3 millimeter ditzel in a patient with a little bit of dyspepsia is more than likely completely unrelated and the 3 millimeter little thing has no clinical significance. And you can't tell them apart from the way that they defined them in this study, unless you look at each one individually, like I did and find out that most of them are the little bitty "nothings."
Q. Did you actually look at the films?
A. They don't have any film.
Q. Are you sure?
A. They don't have any film that I can see --
Q. Okay.
A. -- but they do have descriptions.
Q. So I want to make sure I understand your testimony right here, because in your report at Page 11 you say "The incidence of endoscopic ulcer, whether symptomatic or not, is also subject to bias and manipulation." Do you see that?
A. Uh-huh.
Q. When you're talking about the incidence of endoscopic ulcer, is that the type of ulcer that was

being observed in the CLASS trial?
A. Most of them.
Q. And, so, you're saying whether it's symptomatic or asymptomatic that the calling of that as an "ulcer" is subject to bias and manipulation? Is that what you're saying?
A. No, not the calling of it. The calling is subject to bias. I'll give you another good example of the bias. If you were to take 100 people, normal healthy people asymptomatic and I were to scope them all, how many would have ulcers, "none."
And, so, then I put them on placebo and I scope them after four weeks, what proportion have an ulcer, endoscopic ulcer, well, the answer should be "none." But it's about 8 percent.
Q. What if you put those same people on an NSAID?
A. It's more than 8 percent -- 10 percent.
Q. It sure is more than 8 percent.
A. No, but it's 8 percent when there's nothing there. There can't be anything there. Placebo doesn't cause ulcers. We're talking about big structural abnormalities. And, so you know there's a background.
Q. Of course.
A. No, no. Why of course? Now, if I do that same study --

Q. Because NSAIDs aren't the only things that cause ulcers?
A. No, no, we're talking about them and nothing else. These are normally healthy people. If I'm doing that study or Frank Lanza's doing that study, experts in this field -- and this has been done. When the experts did the studies, they find the frequency of ulcers in placebo group, "zero." When you go out and hire local doctors and you pay them a bunch to do those procedures, "8, 10 percent." So there's a bias for things being present absent, et cetera, size. All those kind of things are bias.
Q. But I'm trying to get behind the bias issue.
A. Then --
Q. No. Wait. Don't go on yet.
A. I'm going to go on to the part of the bias. Remember, if I give you 200-and -- 2.4 grams of ibuprofen, I'm going to get a lot of these local toxic small things. I'm not going to see those in Celebrex. They're acute damage caused by the acute toxic injury. So, you have those.
And, then, I know that you've got more common symptoms. So I look more often and I find those things that are otherwise asymptomatic and meaningless. They have to be there, because A goes with B. So I

can -- before I start the study, I know I'm going to have -- I'm going to win on this outcome whether or not it's real. That's what Vioxx did, was try and increase those numbers.
They did that less here, but they did it; and they're going to find it the same way. So, then, you have to go down and look at the ulcer, how big is it, is it meaningful, et cetera, et cetera. And you can do that, and you'll find out there's a real problem here.
Q. Well, you're not substituting your personal judgment for the judgment of the committee that was adjudicating these events, are you?
MR. SAHAM: Objection, form, foundation.
Q. (BY MR. DOUGHERTY) I think you've already stated you're not going to testify about that at trial, right?
MR. SAHAM: Objection, calls for a legal conclusion, form,
A. I'm not.
Q. (BY MR. DOUGHERTY) Okay. So, I want to get -- I want to separate out the bias and manipulation, because those are loaded terms. I want to make sure I --
A. I wrote a whole paper on that that you have, a whole paper.
Q. Time out --

A. -- full of details.
Q. -- time out. I want to make sure I understand how you're using these terms in this report, okay?
A. Uh-huh.
Q. You've talked about bias, that there is a definitional bias; is that fair?
A. Right.
Q. So there's a definitional bias and there's also some bias that's introduced by the people that are performing the endoscopy; is that fair?
A. Right.
Q. What other bias?
A. And the other bias is that the asymptomatic damage is going to be more common in the NSAID that -- and, particularly, in the ibuprofen group.
Q. So people taking NSAIDs and, in particular, ibuprofen are going to -- based upon the data that we talked about this morning -- are going to have a higher rate of --
A. -- of symptoms and ulcers --
Q. -- of symptoms and ulcers?
A. -- and whether they're related or not. So, they're going to get more scopes because they have symptoms and they're going to find more ulcers because they're there.

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Q. Right.
A. But they're not causing symptoms and they're not clinically significant and they don't predict outcome.
Q. But the NSAIDs are causing the ulcers?
A. The NSAID caused -- is what caused an ulcer, but it didn't cause the symptoms and it's got no predictive value.
Q. The NSAID is causing the ulcer that they found?
A. The NSAID caused what they found, but not the symptoms; and it has no predictive value. And, so, that's why we got away from endoscopic studies.
Q. Let's keep going on bias. There's a definitional "slash" measurement bias. There's a bias introduced by the person performing it and their relative expertise. There's a bias introduced by the fact that the patients that you're examining by scope are on NSAIDs, correct?
A. Right.
Q. And NSAID patients are going to have a higher rate of endoscopically-observed ulcers than non-NSAID patients?
A. Well, particularly the ibuprofen.
Q. And particularly the ibuprofen. All right. Any other bias that you're referring to in this sentence?
A. Well, then, I'm pointing out in the next sentence that none of this stuff is not standardized.

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Q. I'm sorry, none of this is --
A. Is not standardized. It's all arbitrary.
Q. Okay. Manipulation, I want to -- we're done with bias. I want to move to your choice of the word "manipulation." Are you using that word advisedly, in other words, it means something different from bias?
A. Well, it's a form of bias, if you like. You say that "I know this is going to happen and so, therefore, I can -- you know, if a high dose gives you more," et cetera, et cetera, so I can predict outcome, whether or not -- if it's true, true, and related.
Q. But you're not suggesting that there was any manipulation in the CLASS trial, are you?
A. They did not, to the best that I know, accept and design saying "This is going to give us -- increase their events and not ours." They knew that and so they -- you know, they just took us.
Q. Okay. So the answer to my question is and -- for example -- in contradistinction to what you described in the VIGOR trial, the CLASS trial, there's no manipulation of the endoscopic ulcer data. Is that fair?
A. They were much less pushy, yeah. They were not as smart.
Q. Okay. Is it reasonable for a physician to draw

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an association between symptomatic ulcers and the development of complicated ulcers? Is it reasonable?
A. No.
Q. Should they practice medicine as if one can lead to the other?
A. The ulcer complications by and large occur in chronic ulcers and large single ulcers and they're just different than what they typically see. Now, a skilled endoscopist, a skilled ulcer person can do better; but we don't have those doing these.
Q. Let's talk about the primary care physician. Is it reasonable for the primary care physician to treat a patient with a symptomatic ulcer to treat them as if they're at risk for a complicated ulcer? Is that good practice?
A. Today most people when they see something that the endoscopist calls an ulcer is going to stop the NSAID and treat them for the ulcer, no matter what. So that as Dr.- -- whatever the FDA guy said, you know, that -- and, I mean, it could be another bias and, that is, if people had symptoms and they were at risk, they'd stop the drug and then their risk goes away. So it would be a benefit to the person to have symptoms. But I don't think there are any data to support that hypothesis.

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In the old days when we found ulcers we didn't know were there, we didn't even treat them; because we said we didn't know it was there and you found it. "Doctor Clair Voyant," do you know her? A famous woman.
Q. I do know Dr. Voyant.
A. Well, she's the one that -- the only one that can predict the future.
Q. So coming back to kind of the real world, because I understand kind of from a clinical trialist perspective the positions that you've taken, but I really want to kind of drill down into the ordinary physician. Isn't it reasonable for a physician to treat a patient with a symptomatic ulcer as if it's a possibility of them getting a complicated ulcer exists?
MR. SAHAM: Form.
A. Again, a physician -- when -- if a physician sends a patient to get an endoscopy and they say they have an ulcer of any kind, they're going to stop the NSAID and treat that ulcer.
Q. (BY MR. DOUGHERTY) Because one of the things they don't want to have happen is have that patient develop a --
A. Well, that and they're worried --
Q. -- complicated --

A. -- about the symptoms.
Q. Let me finish?
A. They're not worried about the complication, because it's unlikely to occur anyway. Most ulcers don't -- if you have ulcer disease, okay, that means you have an ulcer there all the time and when they look. Your chances of having a complication is 1 percent per year.
Q. So why even study it in a clinical trial?
A. Huh?
Q. Why even study it in a clinical trial?
A. Well, because those are peptic ulcer disease. Real peptic ulcer disease that's there most of the time has only a 1 percent per year complication. And so -- in fact, in Dr. Chan's study, when they looked at the complicated ulcers and they put them on therapy and then they looked at them again, even the asymptomatic ones frequently still had an ulcer.
Q. Were the endoscopic -- were the symptomatic ulcers observed in the CLASS trial at a rate more or greater than or less than you would expect to see in clinical practice?
A. They're about what you're going to see if you scope people at, you know, intervals. I mean, they had a -- the rate of complicated ulcer was about what you

will expect to see.
Q. Among those who were scoped in the CLASS trial, would you expect similar rates of ulcers across all treatment groups?
A. Well, you expect fewer endoscopic ulcers in the Celebrex group, so -- because you expect fewer symptoms and fewer ulcers and so, therefore, you expect if you use that as an outcome to see a difference.
Q. How do you know that?
A. You know that from the endoscopic studies.
Q. The --
A. You can't say that -- I can't say that about Diclofenac, because I don't know about Diclofenac; but I can say that about ibuprofen.
Q. Do you know what the rate was in any of the treatment arms of Class 4 symptomatic ulcers?
A. No, but I know that if I just scoped them all, I would find ulcers in 30, 40, 50 percent.
Q. So when you were answering my question about the differential rate of symptomatic ulcers in CLASS, you were not actually relying on the CLASS data to answer that question. You were relying on the endoscopic studies that had been done. Is that fair?
A. The ones you expect from the studies, the data that you have before you start the study.

Q. Would looking at the actual rates in the CLASS trial change your opinion?
A. Yeah, I mean they had fewer than if you would have done regular endoscopy, because they didn't do regular endoscopy.
Q. Are the rates of symptomatic ulcers observed in the CLASS trial higher than you would have expected?
A. No, no, I don't -- but I'd have to look at the proportion of the patients who underwent an endoscopy had an ulcer to get the proportion that I expect to know what their proportion is, because you have to be tested to know. And the data we have are from people who all got tested.
Q. So what -- just as a percentage-wise -- what would you expect the rate of symptomatic ulcers to be in CLASS for the Celebrex treatment arm?
A. If I looked at everybody?
Q. Well, no, in the actual Class data itself. Because they didn't look at everybody, right?
A. Then I don't know what they should be.
Q. Well, what about Diclofenac or ibuprofen, what should they be?
A. It should be relative to the people who underwent endoscopy. I mean, it should be higher in the ibuprofen than in the Diclofenac, but that's all you know. I mean

you can't say what it's going to be because it depends on did the doctor look and that sort of thing.
Q. The question of bias that you discussed before, potential manipulation, wouldn't you expect those factors to -- if those factors were present in the CLASS trial, wouldn't you expect that the rates of symptomatic ulcers in the class trial would be higher?
A. It really depends on your doctors. You expect them to be -- since it's randomized, you can expect it to be -- because you have more symptoms in the people who are taking ibuprofen, you expect them to be highest. And you have less symptoms in the patients taking Celebrex, you expect them to be lowest. And you expect Diclofenac to be probably more like Celebrex because it's thought to be a safer drug.
Q. I understand that answer and I appreciate it. What I'm trying to do is get you from those assumptions to what the actual results of CLASS were. And I'm trying to understand whether or not the actual rates in the CLASS trial were higher, lower, or about what you would expect outside of the clinical trial setting?
A. I can't -- I don't know what I would really expect. I mean, it's just -- it's hard to know. I think you could only expect the difference between the three groups, not necessarily what the actual number

would be.
Q. Would you expect to look -- would you expect the -- well, let me put it this way: Would you expect the symptomatic ulcer rate in the CLASS trial for Celebrex to be greater than, say, 10 percent?
A. Again, it depends on if I looked at everybody, it should be in that range, 10 or 15 percent. Remember, background is going to be 8 or 9 percent.
Q. The background is going to be 8 or 9 percent?
A. Just because of the flaw in the way they do it.
Q. So, you think because of the bias that you described earlier at a minimum you should see symptomatic ulcer rates in the CLASS data at -- at least 8 percent?
A. If you looked at everybody --
Q. Okay.
A. -- but you're not looking at everybody. The other problem that you have is one more bias in the study, there's a design flaw. I mean, it was a design flaw that came from their mind. You see, they -- and we all -- not just they. They really believed this was going to work.
According to the hypothesis of the preliminary data, this should have worked. And so, therefore, they were willing to take what's called a

"real life" situation without adding all the biases that the other guys in Rofecoxib did and one of the flaws was that it didn't have to be scoped to get into the study. So there was a portion of patients that already had peptic ulcers because they were taking NSAIDs before they got into the study and they -- that was a flaw that, again, is going to increase the number that they're going to see. You'd like to have pristine patients going into your study.
But they really wanted to be able to say "In a real life situation, ignore everything, ignore aspirin, ignore X, Y, Z, that they had H. Pylori, that they had ulcers in the past. This is a completely safe drug." And that's what the hypothesis said. And they tested that hypothesis. You've got to give them credit for that.
Q. Let's talk about the rates.
A. It failed.
Q. Let's talk about the rates. If you assume -- when you read your report, you assumed a background rate of about 8 percent as the starting point for all the treatment groups?
A. If you looked at everybody.
Q. Well, you know that they didn't look at everybody?

A. So, then, you don't have the numbers. You don't know what they are.
Q. Okay. So, would you expect that the rates in the CLASS trial for Celebrex would be above 10 percent?
MR. SAHAM: Objection, form, foundation --
A. I'd have --
MR. SAHAM: -- assumes facts --
A. -- I'd have no way to know. It could be anything. It depends on how often they decided to look. I would suspect that they would be less than ibuprofen and probably less or the same with Diclofenac that's all I can say.
Q. (BY MR. DOUGHERTY) But based upon all your experience, Doctor, and the work that you've done on the endoscopy trials, wouldn't you expect that every single treatment arm is going to have an ulcer -- a symptomatic ulcer rate above 10 percent?
MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.
A. No. Remember that in a clinical trial is done by gastroenterologists. So, they're coming back and seeing the gastroenterologist who will scope you because it's a Wednesday. In this kind of study, they're being seen by a rheumatologists, who's got to refer you over to the gastroenterologist.

Rheumatologists are very conservative people. And, so, you've introduced a different mechanism to manage and to decide when to endoscope the patient. So, you may never see an ulcer just because that's the way rheumatologists are.
Q. I thought you said that you would expect in the CLASS trial the rates of symptomatic ulcers to be similar to the rates that you saw in the endoscopy trials?
A. They would be if I looked. Remember I'm not looking. When we did our studies and you'd ask the rheumatologists "how often do you see the real ulcers, big ulcers in your patients" and then they'd say "we never see it." "How often do they have complications? We never see it." So, we scope them on that day and 15 percent had big ulcers.
Q. But, Dr. Graham, before you can say anything about whether or not the CLASS trial has any bias on the symptomatic ulcer data, wouldn't you need to know the rates, the actual rate? Wouldn't that be important for your opinion?
A. I'm saying that because they're clinically meaningless findings, typically, and because there's this potential for bias, there's no -- and because that the other three events are all real and life-threatening

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and the reason that we worry about NSAIDs, you know, this is over here. All this gives you is noise. It doesn't help you decide this drug, Celecoxib, is better than this drug, which is Diclofenac.

MR. DOUGHERTY: Could you read back my question, please?

(Question read back for the record.)

MR. SAHAM: Objection, asked and answered.

Q. (BY MR. DOUGHERTY) Go ahead, Dr. Graham.

A. It would not be important for the opinion that it would -- that as an outcome variable it's subject to bias, "period." And it's a meaningless outcome variable, et cetera, et cetera, et cetera. So, it really -- you know, I don't care about the actual numbers. Meaningless things are meaningless things.

Q. So, you spent all of your time in this report talking about symptomatic ulcers only to say here today that it's all meaningless?

A. Well, no, that's what he spent all of his time about symptomatic ulcers. So I'm rebutting what he said.

Q. I see.

A. I mean he spent -- that's all he had, I guess. So he spent all of his time about symptoms and ulcers, not important and everybody knows it and, then, you've

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got to be stupid, if you don't believe me. And that's his report. So I say "Well, okay. If that's his report, I'll spend my time saying 'No.'"

I mean, he's a very good rat doctor, a good scientist; but he tended to rock symptomatic ulcers.

Q. I see. So, you want the jury to believe that you can criticize Dr. Wang's report even though you, yourself, have not even done the work to determine what the rate of symptomatic rates were in CLASS?

MR. SAHAM: Objection, form, foundation, assumes facts not in evidence.

A. We know from other similar studies -- many other similar studies what they should be.

Q. (BY MR. DOUGHERTY) What studies are those?

A. The endoscopic studies.

Q. So, you think that the rates observed in the endoscopy studies should be similar to the rates observed in CLASS?

A. No, the proportion should be similar because you have a different reason to look. So if you just took the people in the symptomatic -- in the regular studies and you asked only the ones who went and got off of scheduled time endoscopy, it'd probably be similar to that.

Q. Okay. Doctor, so you're offering opinions

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against Dr. Wang's report -- and, again, we've established that you don't even know what the rates are in CLASS, but you would expect them to be similar to the endoscopy studies; is that right?

A. The actual rates, not the ones they measured.

Q. The actual rates meaning "after"?

A. If it were -- if you asked me -- if I had to predict, if you just asked me to predict, so I would predict -- it's a hypothesis -- that the rates would be the same as the endoscopy studies in the patients who were scoped not at a scheduled time.

Q. The patients in the endoscopy studies who were scoped not at the --

A. Not at the scheduled -- or the off-scheduled because they were symptomatic.

Q. And what would you predict those rates to be?

A. A few percent.

Q. Is that 10 or is that 20? What is a "few"?

A. I don't know, probably less than 10.

Q. Less than 10?

A. 5, something like that; but I don't know. It's just made-up numbers.

Q. Okay.

A. You could look it up.

MR. DOUGHERTY: Scott, can we take five?

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MR. SAHAM: Sure.

THE VIDEOGRAPHER: We're now going off the record. The time is, approximately, 4:35.

(Whereupon, a recess was taken from 4:35 p.m. to 4:39 p.m.)

THE VIDEOGRAPHER: Back on the record. The time is, approximately, 4:39.

Q. (BY MR. DOUGHERTY) Dr. Graham, in the -- at the time that the -- well, let's do it this way: In the last ten years, have you received any money from any pharmaceutical companies outside the context of your expert litigation/expert witness work? And I'm not talking about you personally. I meant to include in that your lab or your work group.

A. Sure.

Q. And can you just list for us the companies that you've been paid by?

A. Well, I'm a consultant for Otsuka, who makes a breath test for Helicobacter pylori.

Q. Do you have a financial interest in the sales of that breath test?

A. I used to get royalties. I don't get royalties anymore.

Q. How much have you made off that urea breath test?

A. Well, a lot.

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Q. What's that?
A. I don't know, all together, maybe 8 or $900,000. Who knows? And we've gotten small potato money from different companies, like -- that help sponsor trials, like we got a couple of thousand dollars from Takeda.
Q. What's your relationship with Novartis?
A. I'm a non-paid consultant to Novartis on their vaccine development. They've actually spent 2 or $3,000 in our lab applying reagents and things. That's, basically, it.
Q. Other than the royalties you received on the Urea breath test and the compensation that you receive in connection with your position at Baylor, do you have any other sources of financial -- do you have any other financial -- any sources of income over the last ten years?
A. My wife works.
Q. I mean based upon your work?
A. Oh, I have other -- we have other patents. We have a patent on the Norwalk vaccine. I just had a paper in the New England Journal last week about that.
Q. Are you getting royalties on that vaccine?
A. Yeah, I've probably gotten 4 or $500.
Q. 4 or $500?
A. So far. Come on. It's only --

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Q. You need a better lawyer, Dr. Graham.
A. Well, no, these are all patents that are at -- Baylor owns the patents.
Q. Baylor does. Okay.
A. We don't own anything personally.
Q. I gotcha.
A. But everything we do is small potatoes.
Q. We talked at the beginning of the deposition about the times that you've been retained and provided expert testimony, and I want to make sure I ask you this question: Have you been retained as an expert in any other litigation, even if you have not yet submitted a report or testified?
A. I've been retained -- they hadn't paid me anything -- for another Canadian one.
Q. Another generic drug company?
A. It's one that I did before that they settled and now unsettled.
Q. Okay. Any other engagements?
A. (Witness nods head.)
Q. "No"?
A. I usually just say "no."
Q. Did you speak with Dr. Patel at any point in connection with your assignment in this case?
A. Who?

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Q. Dr. Patel, do you know who he is?
A. No. I mean I know that Patel means "Gujarati." There's about 50,000 of them probably in Houston here, but I don't know "Patel."
Q. Derek Patel?
A. Huh?
Q. Derek Patel, the gastroenterologist, you don't know him?
A. I know a lot of gastroenterologists named "Patel."
Q. So, I take it, you haven't read Dr. Patel's report submitted on behalf of the Plaintiffs in this case?
A. (Witness shakes head.)
Q. So, you don't know what the other gastroenterologists that the Plaintiffs have hired has said in this case; is that correct?
A. Right. My sanctity is "to tell the truth."
Q. Do you prescribe Diclofenac?
A. I don't think I've ever prescribed Diclofenac.
Q. Okay.
A. You know, it's good for Mickey Mantle, but --
Q. Do you know Dr. Moore, whose paper you refer to in your report?
A. I've met Dr. Moore, but I don't know him.

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Q. Okay. And you took issue with the Moore paper in your report; that is correct?
A. I wrote an editorial about the Moore paper. It was actually the Pfizer paper that Moore and those guys rewrote.
Q. Yeah, you're critical of that aspect of it, Doctor, and if I can just make sure I understand your criticism. Your criticism is that Moore was -- Moore's study was funded by the company?
A. No, no. The company went out and got a vendor to write a paper and, then, they gave it to their advisory committee and asked them if they wanted to turn it into a publishable paper. So, Dr. Moore rewrote it and -- into a more publishable paper or what he thought was a more publishable paper. And the other authors all, at least, read it once.
But it was not necessarily a good paper. It was based upon a compilation of weak correlations and not a carefully reasoned paper. It was one of those ways a drug company is trying to, you know, get messages across.
Q. Well, remember, you're not going to talk about what drug companies are trying to do in this case We --
A. Well, about that paper, it was very clear.

Q. But your criticisms of the paper, Dr. Graham, just so we don't have kind of a drive-by character assassination here, your opinions about that paper are based upon the substance of the paper, not the way it was written, correct?
A. It was well written in English, but it was the substance.
Q. You're criticizing the substance of the paper, not the process by which it came to be published, correct?
A. Absolutely.
(Discussion off the record.)
A. I don't think Dr. Moore is from here. I think he's a Brit.
Q. (BY MR. DOUGHERTY) But that doesn't make him less credible, just because --
A. It makes him less to like when you run into --
Q. An a priori, right?
A. Maybe less like what you see, though.
Q. All right. Did -- Dr. Graham, did the FDA consult you at all in connection with the labeling on Celebrex?
A. They don't consult people about that sort of thing that I know about.
Q. So, the answer to my question is "no"?

A. No.
Q. And are you familiar with the endoscopic ulcer data included in the Celebrex label?
A. I'm -- I'm -- I was in some of the studies.
Q. Excuse me?
A. I participated in some of the studies.
Q. No, I'm talking specifically about the label. Are you familiar with the FDA's conclusion of the endoscopy data in the Celebrex label?
A. I -- I read it once.
Q. Okay. And are you familiar, sir, with the CLASS data that's included in the Celebrex label?
A. I read it once. I didn't pay much attention to it.
Q. Are you offering any opinions in this case about the labeling of Celebrex?
A. I'm not going to offer any opinions currently about the labeling of Celebrex.
Q. Either what's in there or what's not in there?
A. Well, they're all highly negotiated statements.
Q. Do you -- as a matter of practice, Dr. Graham, do you pay much attention to the labels of the drugs you prescribe?
MR. SAHAM: Objection, form.
A. Do I pay much attention? "No."

MR. DOUGHERTY: Okay. Maybe we'll see you again, but thank you for your time, unless Scott has any questions.
MR. SAHAM: No, I think I'll wait.
MR. DOUGHERTY: Wait for trial. Nice meeting you.
THE WITNESS: You guys aren't going to trial, are you?
MR. DOUGHERTY: Not after today. I'm teasing you.
THE VIDEOGRAPHER: This is now the end of tape No. 5 of the deposition of Dr. David Graham. We're off the record. The time is, approximately, 4:48.
(Deposition concluded at 4:48 p.m.)
-- SIGNATURE REQUIRED --

* * * * *

CERTIFICATE OF DEPONENT

I have read the foregoing transcript of my deposition and except for any corrections or changes noted on the errata sheet, I hereby subscribe to the transcript as an accurate record of the statements made by me.

_____
DAVID Y. GRAHAM, M.D.

SUBSCRIBED AND SWORN before and to me this ____ day of _____, 20___.

_____
NOTARY PUBLIC

My Commission expires:

ERRATA SHEET

PAGE	LINE	CORRECTION AND REASON
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(DATE) DAVID Y. GRAHAM, M.D.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
CIVIL NO. 03-1519 (AET)
(Consolidated)
CLASS ACTION

ALASKA ELECTRICAL PENSION FUND, CITY OF SARASOTA FIREFIGHTERS' PENSION FUND, INTERNATIONAL UNION OF OPERATING ENGINEERS LOCAL 132 PENSION PLAN, NEW ENGLAND HEALTH CARE EMPLOYEES PENSION FUND, CHEMICAL VALLEY PENSION FUND OF WEST VIRGINIA, and PACE INDUSTRY UNION-MANAGEMENT PENSION FUND, On Behalf of Themselves and All Others Similarly Situated,
Plaintiffs,

VS.

PHARMACIA CORPORATION, FRED HASSAN, G. STEVEN GEIS, CARRIE COX, and PFIZER, INC.,
Defendants.

REPORTER'S CERTIFICATION OF THE ORAL/VIDEOTAPED DEPOSITION OF DAVID Y. GRAHAM, M.D.
DECEMBER 21, 2011

I, Lori A. Belvin, a Certified Shorthand Reporter and Notary Public in and for the State of Texas, hereby certify to the following:

That the witness, DAVID Y. GRAHAM, M.D., was duly sworn by the officer and that the transcript of the oral deposition is a true record of the testimony given by the witness;

That the original deposition was delivered to MR. JOHN CALEB DOUGHERTY, ESQ..

That a copy of this certificate was served on

all parties and/or the witness shown herein on _____.

I further certify that pursuant to FRCP Rule 30(f)(1) that the signature of the deponent:

____ was requested by the deponent or a party before the completion of the deposition and that the signature is to be before any notary public and returned within 30 days from date of receipt of the transcript. If returned, the attached Changes and Signature Page contains any changes and the reasons therefore:

____ was not requested by the deponent or a party before the completion of the deposition.

I further certify that I am neither counsel for, related to, nor employed by any of the parties or attorneys in the action in which this proceeding was taken, and further that I am not financially or otherwise interested in the outcome of the action.

Certified to by me on this, the 27th day of December, 2011.

_____
Lori A. Belvin, Texas CSR No. 2572
Firm Registration No. 521
Expiration Date: 12-31-2013
Notary Public Expiration: 7-10-2014

COUNTY OF HARRIS)
STATE OF TEXAS)

I hereby certify that the witness was notified on _____ that the witness has 30 days or (_____ days per agreement of counsel) after being notified by the officer that the transcript is available for review by the witness and if there are changes in the form or substance to be made, then the witness shall sign a statement reciting such changes and the reasons given by the witness for making them;

That the witness' signature was/was not returned as of _____.

Subscribed and sworn to on this, the _____ day of _____, 2012.

_____
Lori A. Belvin, Texas CSR No. 2572
Firm Registration No. 521
Expiration Date: 12-31-2014
Notary Public Expiration: 7-10-2014

EXHIBIT 182

From: Wahba, Mona M
Sent: Wednesday, May 03, 2000 11:25 PM
To: Forster, Eliot R
Subject: CBX-0201375_RE: Draft report

You are right on the money. we'll let know tomorrow what is the outcome.

Mona M. Wahba, M.D.
Pfizer Central Research, CRAII
Tel. 860 441 8950
Fax 860 441 3219
Email mona_m_wahba@groton.pfizer.com

-----Original Message-----
From: Forster, Eliot R
Sent: Wednesday, May 03, 2000 3:57 AM
To: Loose, Leland D
Cc: Wahba, Mona M
Subject: FW: Draft report

Leland,

A few comments enclosed int he body of the text.

Generally looks pretty comprehensive. I'm not clear where the line is drawn between those analyses which were pre-defined by the protocol and AP and those added (if any) on seeing the data. If there is a sdifference this should be stated somewhere in the report.

I would like to see more data supporting the assumption that early diclofenac withdrawal due to symptoms reduced the potential for more CSUGIEs in this group as this is central to the agrument about the differential from celecoxib.

Eliot

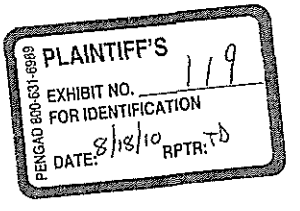
-----Original Message-----
From: Loose, Leland D
Sent: 30 April 2000 16:23
To: Wahba, Mona M; Weiner, Ethan; Zwillich, Samuel H; Christesen, Phyllis M; Finman, Jeffrey; Forster, Eliot R; Frost, R Wayne
Subject: FW: Draft report

Please forward comments to me and I will collate to Searle. Leland

-----Original Message-----
From: DANIEL R. KNIGHT at Exchange
Sent: Friday, April 28, 2000 4:48 PM
To: Loose, Leland D
Subject: Draft report

Leland,

Good afternoon. Aimee and Jim asked me to send you an electronic copy of the



Confidential - Subject To Protective Order

draft of the CLASS report, so it is attached to this message. As I understand,
you will receive the tables by Fed Ex.

I hope all is well in Connecticut (my home state).

Dan

Confidential - Subject To Protective Order